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Theme

Medicinal Plant and Hallucinogens Molecules in Medicine

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بسم الله الرحمن الرحيم

ملخص

يهدف موضوع هته الدراسات الى ابراز دور النباتات ذات التركيبات المهلوسة في المساهمة الطبية الفعالة من خلال تصنيع العقاقير منها مع الاليات السليمة في استعمالاتها تندرج المادة الكيميائية الأصلية للنبات تحت اسم «الدواء العشبي» . بدلاً من اسم الدواء النهائي الحاصل على براءة اختراع..كما ان نقص المعلومات الموضوعية حول النباتات المهلوسات واستخدامها حرمها من التعرف على كيفية هيكلة الاستخدام الآمن لها وتقليل المخاطر وتم استبدال فكرة امكانية ان النباتات المهلوسة. قد تحقق ضررا بالصحة والادراك العام بتغيرها الى النظرة الإيجابية و يمكنها المساهمة في مجال الطب بشكل فعال.لذلك يتم الوعد بتوقع افضل للعلاج بالمواد الطبيعية ، وذلك بفضل التقنيات الحديثة في التصنيع والتحاليل المخبرية مع الالتزام بكافة الشروط السليمة . و تسمح الصيدلة بالنظرفي مجال صناعة الادوية المستخلصة من الطبيعة من جميع جوانب الدراسة في ما يخص الجانب التصنيعي و الكيميائي ، ولكن من المهم مواصلة تعميق البحث باستمرار، و يجب ايضا على المجال الطبي اظهار اهتمام متزايد دوما لمخاطر الاستخدام الغير خاضعة للإشراف في هته التركيبات .

الكلمات الرئيسية : الطب , العقاقير .النباتات ,التركيبات المهلوسة و الدواء العشبي.

Abstract

The topic of this study is to highlight the role of hallucinogenic plants in the effective medical contribution through the appropriate manufacture of medicines.The original plant chemical falls under the name "herbal drug" instead of the name of the final patented drug. The lack of objective information about hallucinations and their use prevented them from learning how to structure their safe use and reduce risk. Therefore, the idea of potential hallucinogenic plants that have harmed health and public awareness through change has been replaced into a positive outlook and can contribute to the field of medicine effectively. There is a better expectation for the treatment of natural substances. Modern techniques in manufacturing and laboratory analysis while adhering to all sound conditions. Pharmaceuticals allow the field of industry extracted from nature in all aspects of the study in terms of manufacturing and chemical aspect, but it is important to continue to deepen research continues, and the medical field must also show an ever-increasing interest in the risks of unsupervised use in those formulations.

Key Words: Medicine, Herbal Drug , Hallucinations Moleculs , Plants.

Résumé

Le but de cette étude est de mettre en évidence le rôle des plantes hallucinogènes dans la contribution médicale efficace par la fabrication appropriée de médicaments.Le produit chimique végétal original relève du nom de « médicament à base de plantes » au lieu du nom du médicament breveté final. Le manque d'information objective sur les hallucinations et leur utilisation les a empêchés d'apprendre à structurer leur utilisation sécuritaire et à réduire les risques. Par conséquent, l'idée de plantes hallucinogènes potentielles qui ont nui à la santé et à la sensibilisation du public par le changement a été remplacée par une perspective positive et peut contribuer au domaine de la médecine efficacement. Il y a une meilleure attente pour le traitement des substances naturelles. Techniques modernes de fabrication et d'analyse en laboratoire tout en adhérant à toutes les conditions sonores. Les produits pharmaceutiques permettent le domaine de l'industrie extraite de la nature dans tous les aspects de l'étude en termes de fabrication et d'aspect chimique, mais il est important de continuer à approfondir la recherche continue, et le domaine médical doit également montrer uneun intérêt croissant pour les risques d'utilisation non supervisée de ces formulations.

Mots clés : Médecine, drogue, Hallucinations Molécules , médicament à base de plantes.

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Appreciation is also given to all those who have somehow helped me achieve this work.

Dedication

I dedicate my dissertation work to my family and every teacher and anyone who has taught me a lesson in this life.

Special sense of gratitude to my loving father Mr. Sai.Chergui and Ms. Zina.Belkhiri

Thanks for always supporting them and pushing for perseverance in my ears. And Thanks to Siblings brothes

" Abde -el-Wahed "; "Mouhamed ";" Chouaibe"

My two grandmothers. Fatima and Khmissa

I also I dedicate this thesis to the late and dear in my heart. Mr. Chergui Boudjemaa and Mr. Belkhiri Larrbi , I would have been the eldest granddaughter in your presence today with me and I would always continue your memory in my heart.

He also gave it to each family Chergui member and family Belkhiri.

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List of Abbreviations

AA	Arachidonic acid
CNS	Central nervous system
2C-C	2,5-dimethoxy-4-chlorophenethylamine
2C-D	2,5-dimethoxy-4-methylphenethylamine
2C-I	2,5-dimethoxy-4iodophenethylamine
DAG	Diacylglycerol
DMT	Dimethyltryptamine
DOB	1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane
DOC	2,5-dimethoxy-4-chloroamphetamine
DOI	(R)-(−)-DOI;(−)-2,5-dimethoxy-4-iodoamphetamine hydrochloride
DOM	1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane
EEC	The European Economic Community
ENT	is the abbreviation for otolaryngology. Medical Specialty studying “ear-nose-throat-larynx” disorders (upper airway)
ERDF	European Fund development is one of the manifestations
ESCOP	the European Scientific Cooperative for Phytotherapy
EU	European Union
FDA	Food and Drug Administration
5-HT	5-hydroxytryptamine (serotonin)
5-HTP	5-hydroxytryptophan
LC	The locus coeruleus
LSD	Lysergic acid diethylamide
MAO	Monoamine oxidase
MDMA	3,4-methylenedioxy-N-methylamphetamine
NBJ	nutrition business journal
NMDA	N-methyl-d-aspartic acid
OCD	Obsessive–compulsive disorder
PA	Phenethylamines
PCP	Phencyclidine
PIP2	Phosphatidylinositol-4,5-bisphosphate
PLC	Phospholipase C
TA	Terptamine
THC	Tetrahydrocannabinol
UNIDO	United Nations Industrial Development Organization
W.H.O	The World Health Organization

INTRODUCTION

Generale Introduction

If herbal medicine has an extraordinary popularity throughout the world, it is impossible to see here only a fashion phenomenon. Of course, our time is profoundly marked by the search for a healthier life, a return to nature, to essential values. But the success of the Herbal Medicine is explained above all by the level of technical and scientific mastery that is now achieved in this field. Agronomy, chemistry and pharmacology have made it possible, through progress, to develop safer, more adapted and more effective therapeutic and clinical forms. By its gentle and in-depth action, Herbal Medicine appears on the other hand as the ideal response to the "diseases of the century" that characterize our societies.

The herbal drug is a "complex" of molecules, derived from one or more plant species. Many clinical forms are now offered, some more innovative than others, leaving the original infusion more or less obsolete**. (Wichtl M & al., 2003)** . Yet these shape changes can sometimes hide changes in the action on the metabolism or bio-availability of the active ingredients.

Early man tried all kinds of plants. Some nourished him, some, he found, cured his ills, and some killed him. A few, to his surprise, had strange The effects on his mind and body, seeming to carry him into Other worlds. **(Richard Evans Schultes & al.,1963)** .We call these plant hallucinogens, because they distort the senses and usually produce hallucinations-experiences that depart from reality. Although most hallucinations are visual, they may also involve the senses of hearing, touch, smell, or taste- and occasionally several senses simultaneously are involve.

The actual causes of such hallucinations are chemical substances in the plants. These substances are true narcotics Contrary to popular opinion, not all narcotics

aredangerous and addictive. Strictly and etymologically speaking, a narcotic is any substance that has a depressive Effect, whether slight or great, on the central nervous system.

Narcotics that induce hallucinations are variously Called hallucinogens (hallucination generators), psychotomimetics (psychosis mimickers), psychotaraxics (mind disturbers), and psychedelic (mind manifests). No one term fully satisfies scientists, but hallucinogens comes closest. Psychedelic is most widely used in the United States, but it combines two Greek roots. **(Safford. & al., 1917).** incorrectly, is biologically unsound, and has acquired popular meanings beyond the drugs or their effects.

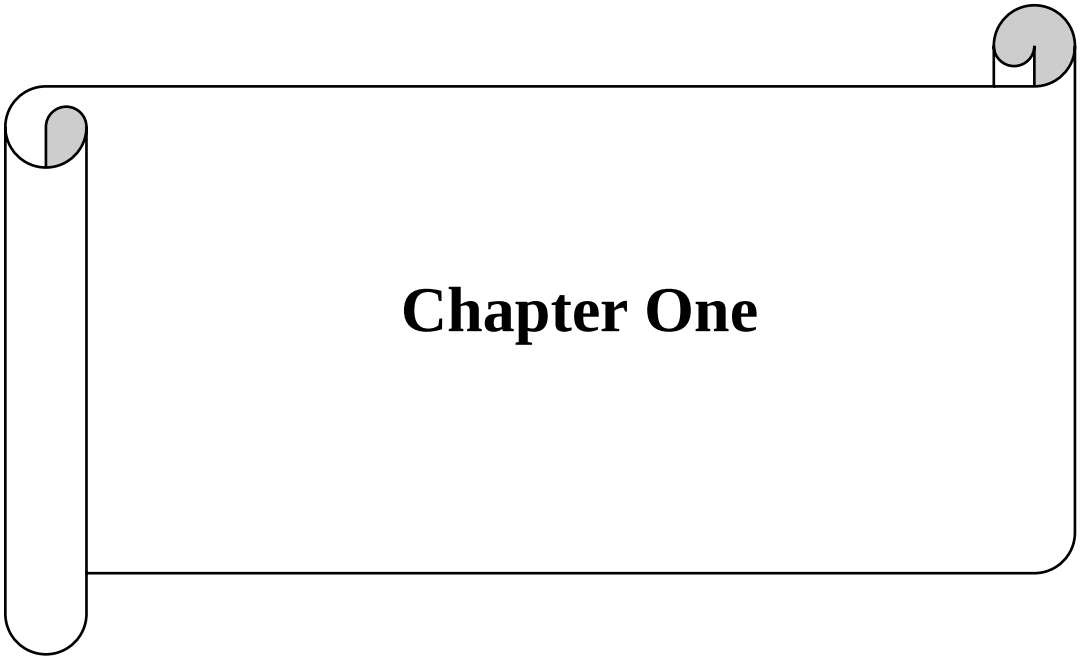
This work is devoted to medicinal plants, hallucinogens and their advice for medical use. It therefore contains all the list of plants used in medically owned medicinal products, as well as all the forms in which plants are naturally found by medical and pharmaceutical products only. Moreover, it has no claim to complete the exceptional mass of medicinal plants used in medicine in general. The main purpose is to establish a list of the various forms used in the medical field, with the most appropriate counselling for each type of medication .

Our work consists of five main research axes:

- **The first chapter :** General information on medicinal plants and hallucinogens plants
- **Chapter Two:** Herbal drugs and the importance of scientific investigation.
- **The third chapter:**Parts of the plant to be used, nomenclature, purchase and conservation of medicines.
- **The fourth chapter :** Mode of action hallocinogens moluculars.

- **The fifth chapter :** General effect of hallucinogenic drugs drug impact mechanism.

The conclusion contains the results obtained in the studies adopted in the previous chapters.



Chapter One

1. Introduction

Plants impose themselves on the planet by their appearance and branching out their use in the fields of life.From early times, man sought a way to satisfy his hunger. He found nutritious foods in plants, but also treatments for his diseases, learning the hard way to distinguish toxic plants. This knowledge, first transmitted orally, was then in the literature and there are still traces of the use of plants as medicines by the ancient in the oldest civilizations.

2. History

Richard Evans Schulz wrote two decades ago: Many of our official medicines have come accidental to the work of individual botanists involved in some of the larger projects, and I am convinced that most of the discoveries will be made by botanists and ethnic botanists **. (R. E. Schultes,1963)**. Or anthropologists participated leisurely in their own research rather than in expeditions sent to find new medicines. We must not underestimate or lose sight of the role played by the average person in the past and present.

About three centuries have elapsed since one of the earliest introductions to recorded botanism was published, in four pages, by Leonhardt Fox, an educated physician in Toppingen.

The term ethnobotany was first used in 1895 by Harshberger **.(J. W. Harshberger,1895).** Introduction to Ethnobotany by Faulks was perhaps the first book specifically on the subject**. (P.J. Faulks, 1958).**Studies and publications on " ethnobotany " during the last three decades have stimulated many lines of interdisciplinary research under more specialized titles like ethnopharmacology, ethnomedicine, ethnogynaecology, ethnopaediatrics, ethnobiology, ethnozoology, paleoethnobotany; separate journals devoted to some of these disciplines are now published.The recent rediscovery of the remarkable properties of plants has given new life to a multidisciplinary science: ethnobotany_ an ethnic plant deals with direct**.(R. I. Ford, 1978).**

The term is often considered synonymous with economic botany or traditional medicine. Economic botanism is concerned with the use and trade of processed, improved or otherwise modified plant products by man**.(S.K.Jain;1986)**.

3. Botany In Primitive Societies

3.1.The 'Age of herbals' in at The early days .

The period between the 15th and 17th century AD in Europe was regarded as the 'Age of herbals'. In that time, plants were by far the most utilized (and often the only available) treatment modality for human disease **(Goldman, 2001).** Notably, most early herbalists were both physician and botanist. Many physicians, particularly those from the Mediterranean region, followed Dioscorides, while German and Dutch physicians consulted 'wise women' - witches - to broaden their knowledge of medicinal plants. Among the most popular herbals were the anonymous '**Grete Herball'** (1526), Gerard's 'The Herball or General history of plants' (1597), and Culpeper's 'The English physician enlarged' (1653).

One of the 'scientific' methods most widely employed in those days for identifying plants with medicinal properties was the 'doctrine of signatures' **(Bennett & al.,2007)**. This concept was developed by Paracelsus, professor of medicine at the University of Basel, Switzerland, in the first half of the 16th century, and is a religious or spiritual system of beliefs according to which God put plants on Earth for the benefit of man, and marked them with a 'signature' that identifies their purpose **(Bennett & al., 2007).**

Despite the availability of enormous weapons of medicines, cardiovascular and malignant diseases, diabetes, airway and infectious diseases remain among the leading causes of morbidity and mortality in many parts of the world **(Lopez & al., 2006).**

These considerations led to a reassessment of an "old" but successful strategy for the acquisition of highly therapeutic candidate compounds: assessment of plant-derived substances **(Cragg & al., 1997**). Indeed, the impressive diversity of plants' diverse chemicals may result in a large number of new and more effective drugs against human diseases **(Cragg & al., 1997) .** Botany for more than half a century in its contribution and the development of new drugs from the systematic discovery and development of medicines has established many useful medicines as well as a large number of successes in the treatment and management of human diseases.

4. Medicine From Plant Sciences

Currently preserved clay discs stand out at The British Museum in London. These documents were copied from the Sumerian, Akkadian and Babylonian ages (around 4000 B.C.) by order of Assurbanipal (the period of 668-627 B.C. rule) in cuneiform in the seventh century B.C. We also know that Sumerians were already using myrtle, cannabis, other and Willow in dismantling a refinery **(Bézanger-Beauquesne L & al., 1975.)** . This inscription represents the first known text on the medicinal properties of plants.

Already around 2000 BC, the Assyrian king Hammourabi (period of reign 1792-1750 BC) encouraged the cultivation of medicinal plants.Moreover, in 1600 B.C. the Egyptians were said to have used several hundred drugs . A famous papyrus, the Ebers Papyrus, is one of the largest known. It contains 108 pages on diseases and their remedies by plants **.(Paris R.R & al., 2008)** . The German Egyptologist Georg Moritz Ebers (1837-1898) studied it himself with remarkable skill, and translated and commented on a part of it; Dr Heinrich Joachim (1860-?), Gave a complete and skilfully annotated translation of it in 1890. The Ebers Papyrus, formed itself by the gathering of several small treatises, was, according to calculations based on serious bases, composed and written around 1550 B.C.

The study of the ancient Chinese, Hindu and, in the New World, of the Aztecs of Mexico and the Incas of Peru, shows an extensive knowledge of medicinal and toxic plants. The closest to us, the Greeks inherited, in the same way, some eastern drugs across the Persians. They had great doctors, such as Hippocrates (460-377 BC) and Aristotle (384-322 BC) who used drugs (opium, Joskiam, Mandragura) .(Starck V). Theophrastos (whose real name is Tertamus) was called the Theophrastos "divine speaker" (371-286 BC), In his thesis on the history of plants, he left the precise plant descriptively . But Discorides (about 40-90), a Greek born in Asia Minor, is the real ancestor of medicines. Travel to Egypt, Africa, Spain and Italy. His thesis, dating back to 77 and translated into Latin in the 15th century under the title "de Materia medica", Inventories of 500 medicines of plant, animal and metal origin. This work spread throughout the Roman and Arab world and had a significant impact until the end of the Middle Ages.

Among the Romans, Aulus Cornelius Celsus (25 BC-50) described 250 drugs. Pliny the Elder (23-79) reported in several volumes of his Natural History the medicinal virtues of plants. Claudius Galenus they call it Galien (131-201), considered to be the father of the

drugstore, gave recipes for the preparation of medicines; he influenced Western medicine for centuries.After the fall and dismemberment of the Roman Empire, Western Europe went through a period of obscurantism (5th to 11th century) during which magic and witchcraft dominated the use of plants. (Encyclopédie universelle de la langue français).

However, an edict of Charlemagne (742-814), in the Capitulars of Villis (circa 800), advised the cultivation of medicinal plants. This included the main list of plants concerned, a total of 94 plants: 73 herbs, 16 fruit trees, 3 textile plants and 2 tinctorial plants(A plant or mineral used to create dyes for tissues). This text does not in itself represent an agricultural revolution, because all the plants he cites were long known (Encyclopédie universelle de la langue français).but Charlemagne tried to raise the intellectual level of the clergy by creating religious schools where the study of healing plants was the basis of medical teaching.

Priests and monks maintained these cultures around the monasteries in the garden of the "simple". They studied plants and remedies in general, transcribing and commenting on the works of Aristotle, Hippocrates, Dioscorides, Galian, Pliny, etc. They experimented themselves in their gardens based on this book knowledge and custom. It should be noted, however, that at that time only religious were the holders of the knowledge of the Latin language (Greek is little known except to some scholars) which ensures the transmission of the ancient pharmacological heritage. The garden of monasteries becomes, par excellence, the place of cultivation of medicinal plants**.(Chabrier, J. Y. 2010).**

As an example we can observe the organization in 850 of the garden of the simple (herbularius) of the abbey of St.Gall, which will be a model for the vast majority of abbeys until the eighteenth century .

4.1. St. Gall's plan

St. Gall's plan is the oldest preserved and unusual conception of a building complex produced in the Middle Ages. St. Galle's plan was drawn and hung on five pieces of slavery sewn together, 112cm × 77.5cm and includes floor plans for about forty buildings as well as gardens, fences, walls, road and orchard. Three hundred and thirty-three inscriptions identify buildings and their uses, including the church. Scriptorium, visiting monks' residences, monks' dormitory, restaurant, kitchen, bread house and drink, guesthouse, monastery head's

residence, infirmary, many fields and industrial outdoor buildings. The gardens were designed for contributions to pharmacology and botany.

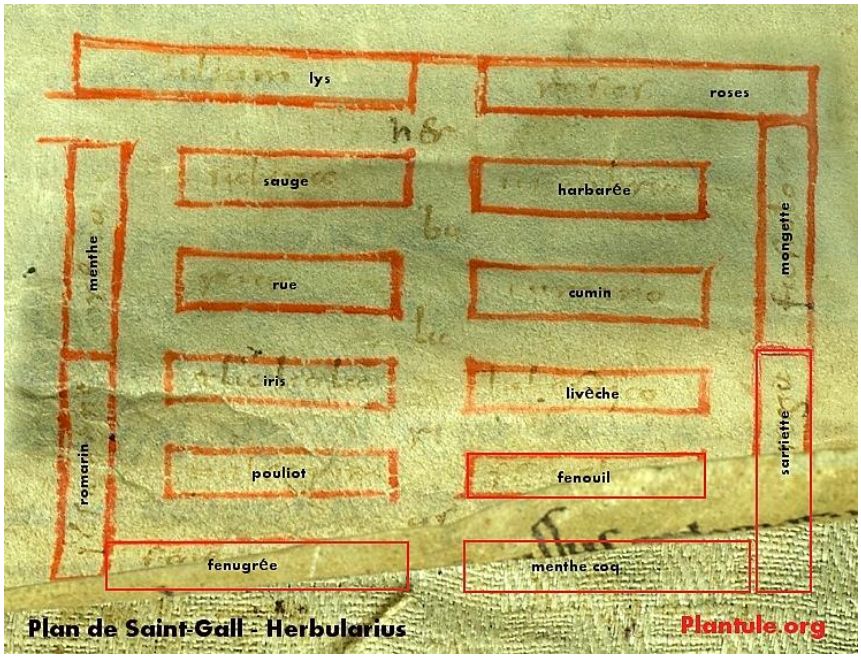


Figure 01 : Planning structure for the engineering and distribution of plants in St. Galle's Monastery Garden **. (Chabrier, J. Y. 2010).**

Table 01: A table representing the varieties and names of plants grown in St. Gall's monastery and their family branches **. (Chabrier, J. Y. 2010).**

English name	**Latin name of the St Gall plan**	**Latin name of the Chapter of Villis**
Cumin	*Cumino*	*Cimino*
Fennel(Foeniculum vulgare)	*Feniculm*	*Fenicolm*
Fenugreek	*Fena Graeca*	*Fenigrem*
Iris	*Gladiola*	*Gladiolm*
Lovage;Levisticum officinale	*Lubestio*	*Levisticm*

Lilies	*Lilium*	*Lilium*
Mentha	*Menta*	*Mentam*
Mentha aquatica (water mint)	-	-
Tanacetum balsamita	*Costo*	*Costum*
Mentha pulegium	*Pulegium*	*Puledium*
Catjang(Vigna unguiculata subsp. cylindrica)	*Fasiolo*	*Fasiolum*
Barbarea verna Common names include land cress, American cress, bank cress, black wood cress, Belle Isle cress, Bermuda cress, early yellowrocket ,early wintercress, scurvy cress, creasy greens, and upland cress	*Sisimbria*	*Sisimbrium*
Harbarée according to the plan shown previously but unknown.		
Rosemary ; Salvia rosmarinus;Rosmarinus officinalis	*Rosmarino*	*Ros marinum*
Rose	*Rosas*	*Rosas*
Ruta (commonly known as rue)	*Ruta*	*Rutam*
Salvia ; sage .	*Salvia*	*Salviam*
Satureja	*Sataregia*	*Satureiam*

5. From Forest To Pharmacy Plant

The Pharmacy, which is responsible for the identification and testing of drugs, as well as the preparation of drugs, then separates from Medicine. They used to be exercised by the same people. It was not until 1777 that Louis XVI distinguished the two fields and finally specified that pharmacy is a matter independent of medicine which also requires a serious and in-depth learning. The word "apothecary" then disappeared to give way to the name "pharmacist" **.(Lafont. O, 2007)** . We enter the scientific period, based on observation and experimentation. A solid basis for the use of natural products could only be found after isolation and study of their active ingredients.

Thanks to the alchemists, in search of gold, many substances of mineral origin were known in the sixteenth century. But certain chemical principles were not to be removed from the plants until the end of the 18th century, when the Swedish pharmacist and chemist Carl Wilhelm Scheele (1742-1786) separated the first organic acids (oxalic, malic, tartaric, etc.)

At the beginning of the 19th century, in 1803, Jean-François Derosne (1774-1855) managed to isolate a salt from opium: Derosne salt, a mixture of narcotine and morphine**.(Pol D & al.,1788-1842)** and Joseph-Bienaimé Caventou (1795-1877) **;(Kerharo J & al.,1950).**

The way to alkaloid chemistry was open.At that time, the first heterosides were also separated, such as the Salicin du Saule, which was discovered by Pierre-Joseph Leroux (1795-1870) in 1830. This was also the case in the same year of the amygdalin of bitter almonds, which was extracted by chemist Pierre Robiquet (1780-1840). As for the crystallized digitaline, it was separated in 1868 from the Digitale purple by the chemist pharmacist Claude Adolphe Nativelle (1812-1889**).(Paris R.R & al.,2008).**

Advances in chemistry made it possible to know the composition of the plants and to gradually establish the notion of active ingredient.A new aspect of the study of drugs was to arise with the development of Physiology. In France, this progress was mainly due to the work of Claude Bernard (1813-1878). It was tests on animals that made it possible to verify the activity of plants used for a long time in popular medicine and to specify their mode of action on a given organ.The correlation between the chemical structure of the constituents and

the physiological action (modern version of the theory of signatures) became apparent towards the end of the 19th century.

This great scientific advance led to the discovery of substances having important physiological activities and existing only in the state of traces: vitamins, hormones, antibiotics and antimitotics, is how the three aspects of modern medical matter gradually emerged. The first is presented as the botanical examination of drugs, often sufficient for their identification. The second is the study of their chemical composition and in particular of their active principles. And to finish the study of their physiological activity, which conditions their use in therapeutic .

"Pharmacognosia", developed almost exclusively in the botanical sense until the early 20th century. Indeed the descriptions of the active parts of the plants were initially purely morphological. **.(Aiache J.-M & al., 2008).**They concern not only the drugs themselves, but also their falsifications. Then microscopic characters were introduced into recognition and expertise. This part of the Medical Matter always remains fundamental since, without precise botanical determination, there are no valid chemical and physiological studies.But the chemical constituents of plants require to reserve for them an increasingly extensive place in the modern Treaties, and this, because of the strong development of Science. This is also the case of their physiological properties (this appears in France especially in the works of Joseph Herail (1857-1940), late nineteenth century, which were then followed by many others). Subsequently, it is the turn of the conditions of production and cultivation of plants to take an ever greater extension, but also the introduction of exotic species, the normalization of drugs, as well as the trial that benefits from the progress of analytical chemistry.

It should also be noted that the use of many different exotic plants has necessitated the creation of collections containing reference samples. **(Nicolas Jean & al.,1790-1867)**, At the beginning of colonial history, the main purpose of the study of plants was to provide the metropolis with useful food and industrial products of tropical origin.As the European crop trials have failed, these plants need to be grown in their countries of origin or transplanted to our colonies in similar soils and climates. Spices, precious woods, tinctorial plants, then cotton, rubber, coffee and cocoa, rice, etc. harvested in its colonies guarantee France a constant quality and total independence of its supplies.

It is also a question of discovering, in this unknown flora, new drugs to strengthen the therapeutic arsenal used at the end of the 19th century. Very quickly, the medicinal plants used by healers are the subject of research and sometimes allow the development of drugs.By 1910, however, the development and early success of chemical synthesis relegated natural substances to the background. From 1935, a new interest was shown in the analytical study of tropical plants, particularly those known to have pharmacological properties. (Perrot R).. In the front row are traditional poisons, fishing poisons, arrows for hunting or war, trial poisons used for justice or initiations. **(Kerharo J & al.,1950).**

In the last 50 years, thanks to the progress of analytical methods, our knowledge of plants has increased considerably. Many reviews of bibliographic extracts contain a considerable number of publications relating to the isolation of new constituents in plants, the detailed study of their chemical structure, their physiological properties or their formation in the plant. Even in drugs very formerly known and used for centuries like Digitale, we discover new principles and properties. The "good woman's remedies" are often the starting point for fruitful investigations. Indeed, it was originally written "remedies of good fame" (from the Latin "bona fama"), that is, of good fame. The connotation was therefore not pejorative, as we know it today. Then the use of the word "famé" was lost over time, and it was replaced by the word "woman" denoting the woman in popular language, often uncivil**. (Guillemard C. 2007)** .

In Europe, the Pharmacopoeia consisted mainly of plants until the end of the 19th century. They were not really replaced by synthetic drugs until after the Second World War (there were nearly 4,500 herbalists in France in 1941) **.(Chabrier, J. Y. 2010).**

Despite the advances in chemistry which have made it possible not only to isolate the active ingredients in their pure state, but sometimes to synthesize them completely and obtain artificial active substances in almost unlimited quantities, plants have retained their importance.The action of the plant is not always that of the pure isolated product. The plant drug, originating from living matter, is generally better tolerated by the body than many synthetic substances, physiologically very active, but whose side effects are sometimes unpredictable**.(Schultes, Richard Evans; 1973).**

The study of plants has progressed over the centuries. Yet the pleasure of seeking in the plant world that is offered to us what can relieve physiological problems has not been

excluded by the scientific era of herbal medicine.As for curiosity, which constantly pushes back the limits of the unknown thanks to the perfecting of analytical methods, it is entitled to claim countless discoveries.Transmitted by experience, accredited by the study, multiplied by prospecting, medicinal plants have retained the prestige of the oldest remedies and also retain an inexhaustible potential. However, their share is subject to inevitable variations. Indeed economic contingencies can lead to the temporary disappearance of the market of some plants while others impose themselves on the therapeutic as new conquests or revaluation of old drugs. The role of the pharmacognost is therefore to update periodically this development intended to place all those who are interested in the reality of the facts.Yet the many acquired points remain minute compared to the domain of the unknown. Many plants have never been studied, or have not been studied by modern methods. There is an immense field of possible investigations, constantly expanding and renewing the field of medical matter**.(Fabricant DS & al.,2001).**

6. Hallucinogens at the turn of the century

"Gods plants" is a term that refers to the religious meaning of members of many primitive cultures around the world attributed to plants containing hallucinogenic or mind-changing substances. Dr. WE Dixon, well-known British pharmacologist of his time, once commented that narcotic indulgences reflect the sad paradox that humans seemed to get their ‘‘chief pleasures in life by escaping out of life’’ **(Narcotic Plants, 1928: 252).** There may be truth to this as narcotic/sedative effects were commonly sought for by various cultures, second to hallucinogens, with members of Papaveraceae and Lamiaceae traditionally used for this purpose. Opium poppy of Papaveraceae has long been known to ancient Greeks and Sumerians and is considered one of the most important medicinal plants in history. Its opium latex is the source of >30 alkaloids including morphine and codeine, which bind to opioid receptors, promoting sedation and analgesia **(Heinrich & al., 2012).** Though there are other members of Papaveraceae that have been used by Asians and Native Americans for sedation and pain relief **(Rolland & al., 1991). (Brahmachari & al.,2013).(Shang & al., 2015),** the substances responsible for their effects are not well characterized as in opium poppy, but it is possible that their effects are also mediated via opioid receptors **(Shang & al., 2015)** and at least in Eschscholzia californica **(Fedurco & al., 2015).**

Hallucinations permeate almost every aspect of life in primitive societies. They play roles in health and disease, peace and war, domestic life and travel, fishing and agriculture; It affects relationships between individuals, villages and the tripartite. They are thought to affect prenatal and post-mortem life in old beliefs , Humans have been using hallucinogenic plants for thousands of years, perhaps since they began collecting plants for food. Hallucinogens continued to receive. **.(Hoffer & al., 1967).**The attention of civilized man through the ages. Recently, we have been through a period during which evolving Western society has discovered hallucinogens and addressed some sectors of this society.

For one reason or one reason, use these plants Nevertheless, centuries of trial-and-error experimentation by shamans, herbalists, witches, alchemists, and other practitioners, inevitably lead to the discovery of the biodynamic properties of certain plants, and of these, it was plants affecting the nervous system and mental functions that often had the most profound and dramatic effects; the juice of certain poppies had the power to block pain and induce a dream-like sleep; chewing the leaves of other plants could induce a state of wakefulness and mental clarity; consumption of certain mushrooms or seeds could plunge the eater into a bizarre alternate reality, complete with visions, voices, and confrontations with gods (or demons) **.(Pelt J M , 1971).** Given the unambiguous and occasionally terrifying effects of psychoactive plants, whether consumed accidentally or deliberately, it is little wonder that our ancestors early on developed a healthy respect for the power of plants to heal, as well as to derange and evento destroy.

Hallucinogens, including those derived from plants, are a special case when discussed in relation to psychotherapeutic drug development**.(Safford, William E ,1917).** Except for a small cadre of radical psychiatrists and therapists who are generally regarded as out of the mainstream, the notion that hallucinogens may be a reasonable therapeutic option in certain situations is not an accepted tenet of Western medicine, despite an abundance of anecdotal evidence from shamanic traditions indicating that hallucinogens can frequently be efficacious in attenuating the causes(or at least the symptoms) of psychological disorders, if not physical illnesses While the potential therapeutic value of the psychedelic experience briefly attracted the attention of the psychiatric community several decades ago, efforts to develop a 'scientific' validation of hallucinogen therapy have been largely abandoned.

Investigation of the human psychopharmacology of hallucinogens may provide investigators with pharmacological models of mental illnesses. The notion that the hallucinogenic experience is a 'model psychosis' dates from the middle of this century, when it was first suggested by Osmond and Smythies Osmond**.(Osmond, H. & al.,1952).** Clever practitioners adapted the use of psychoactive and other biodynamic plants to their own purposes incorporating them into quasi-medical practices as well as ceremonial and magical activities; gradually, people became more sophisticated in the herbal arts, sharing and transmitting the secrets of plant-lore between cultures and generations. New methods of preparing sophisticated, multicomponent 'recipes' were discovered as were new technologies for extracting the 'essences' or spirit' of the plants. The discovery of steam distillation in the Middle Ages**.(Stoll, M , 1967).** was one such turning point, as it marked the appearance of one of the first pharmaceutical technologies that went beyond the preparation of simple aqueous decoctions (as well as enabling and fostering the development of perfumery). he use of hallucinogens is widespread in cultures which assigned positive meaning to the experienced altered state of consciousness, such as allowing the user access to the spiritual world**.(Júnior & al., 2015).** Hallucinogens used in divination and religious healing (i.e., entheogens) may have played a significant role in human evolution **(Schultes & al.,2001).** Native Americans prolifically used hallucinogens, but hallucinogenic use seems to be lower in temperate Asia. Increased hallucinogenic use among indigenous peoples of Brazil South America. **(Rodrigues & al., 2006)**.

6.1. The Kingdom's plant family tree and branches throughout history

Interestingly, humans exploited alternative uses of plants containing psychoactive effects.phytochemicals that have allegedly evolved to ward off plant predators. However, the convergence of these plant chemicals within the human nervous system may also indicate some A kind of mutual mutual evolution, with ancient human endeavours and possibly cultivation Plant psychotropic substances to facilitate survival, by alleviating hunger, fatigue and pain **(Sullivan & al., 2002).**

It is well established that all cultures, ancient or modern, have some kind of drug culture, relying on psychoactives for recreational, ritual and/or medicinal use**.(Schultes, 1976); (Schultes & al.,2001)**. Shamanistic religions have existed in the Old World of Europe, Asia and Africa, believing that psychoactive plants are capable of healing through divine power. Marijuana (Cannabis spp., Cannabaceae) and opium poppy are among the most popular

psychoactive plants used by Old World shamans. Marijuana was used in ancient China for various afflictions like malaria and constipation, and even as a narcotic in surgeries. In India, the plant was considered sacred promoting pleasurable sensations in the user **(Clarke & al.,2013).** Tetrahydrocannabinol (THC) in marijuana, exerts these actions by binding to cannabinoid receptors, mediating sensory pleasure **(Mahler & al.,2007).** Another familiar psychoactive, opium poppy was used for medicinal and recreational purposes. It probably originated in the Mediterranean, but widespread use has confounded its evolutionary origin **(Merlin, 2003).** It was recorded in the Eber papyrus, an ancient Egyptian scroll, that opium poppy was used to stop the excessive crying of children **(Vetulani, 2001).** The plant contains morphine and codeine that are responsible for its hypnotic and analgesic properties **(Heinrich & al., 2012)** .

Indigenous people of the New World have also used psychotropic substances, including tobacco, ayahuasca, and coca, even more so than cultures of the Old World (Schultes, 1976). Tobacco from the leaves of N. tabacum has long been used in the Americas, with cultivation in pre-Columbian Mexico or Peru **(Rätsch, 2005).** American Indians believed in the medicinal power of tobacco, and it was smoked in ceremonial peace pipes to seal covenants. In the Amazon Basin of South America, the hallucinogenic beverage, ayahuasca, is made by healers from the boiled crushed stems of the caapi, Banisteropsis caapi (Malpighiaceae), along with the leaves of chacruna, Psychotria viridis (Rubiacea) ; Chacruna contains serotonergic N, N-dimethyltryptamine (DMT), that is activated by the beta-carbolines in caapi **(McKenna, 1996)**. In the Andes, indigenous peoples chew coca leaves of Erythroxylum coca (Erythroxylaceae) to cope with hard labor, removing symptoms of fatigue and hunger (Nigg & Seigler , 1992). Its cocaine content prevents dopamine reuptake producing increased energy and mood elevation **(Spinella, 2001)** ; The 126 psychoactive seed plant taxa belong to 56 families and 31 orders and together comprise 1.6% of the total generic diversity for these families. The phylogeny reflects expected relationships**.(APG IV, 2016).**

The phylogeny con- forms to expected groupings **(APG IV, 2016).** The 11 main plant families are highlighted (top to bottom): Myristicaceae, Papaveraceae, Malvaceae, Fabaceae, Cactaceae, Asteraceae, Convolvulaceae, Solanaceae, Lamiaceae, Rubiaceae, Apocynaceae. Grey circles next to their family names are proportional to total generic diversity within the family with lowest count for Myristicaceae (21 genera), and highest with 1623 genera for Asteraceae **(Christenhusz & al.,2016).** Branches are coded according to the different cultures

(Native American: red solid line; Middle Eastern and African: orange dashed line; European: blue solid line; Indomalayan: green dotted line; Temperate Asia: pink solid line, Australasia: yellow solid line; Multi- cultural: grey solid line). Branches in bold represent bootstrap node support >50% and SH-like branch support >0.9.

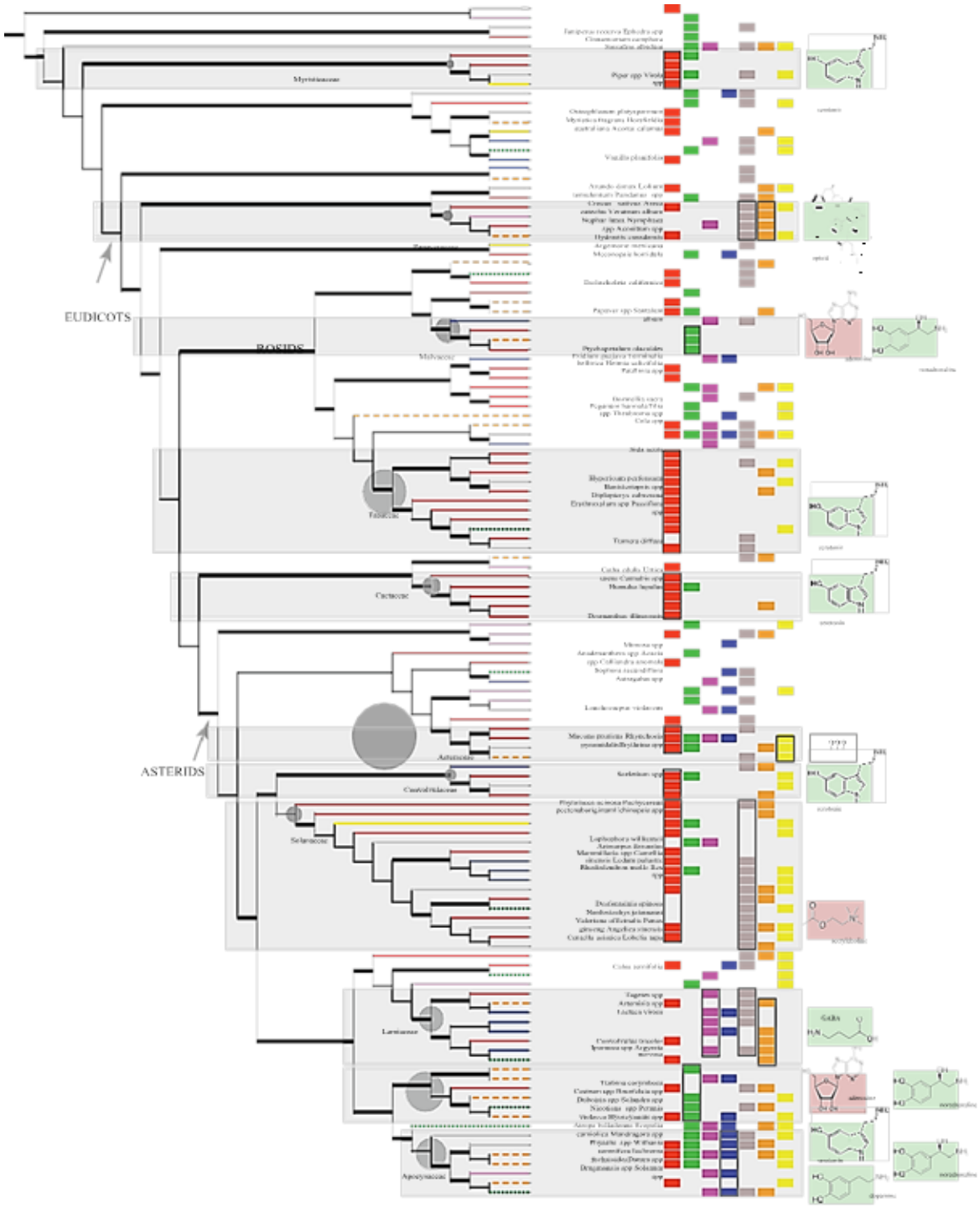


Figure02: The phylogeny (cladogram) of traditionally used psychoactive plant taxa.

(APG IV, 2016).

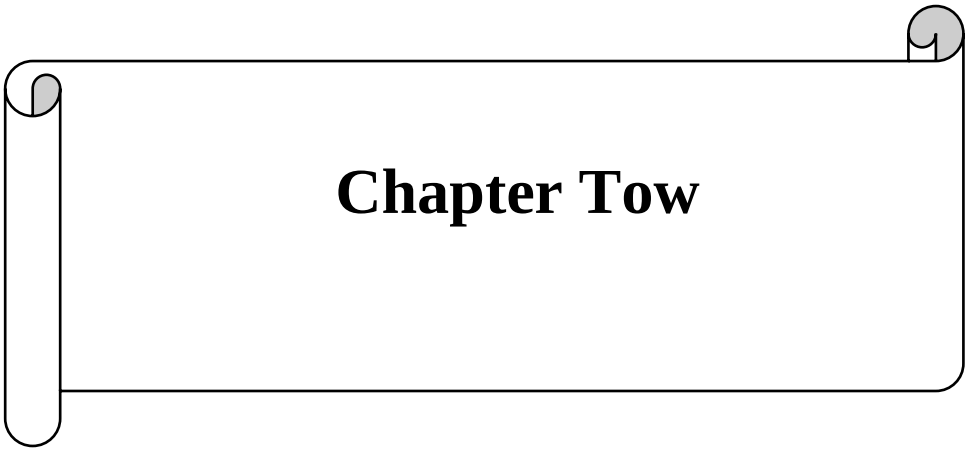
7. Hallucinogens plants based drugs and medicines

Psychoactive plants contain chemicals that presumably evolved as allelochemicals but target certain neuronal receptors when consumed by humans, altering perception,emotion and cognition**.(Schultes, Richard Evans & al.,1973)** . These plants have been used since ancient times as medicines and in the context of religious rituals for their various psychoactive effects (e.g., as hallucinogens, stimulants, sedatives). The ubiquity of psychoactive plants in various cultures motivates investigation of the commonalities among these plants, in which a phylogenetic framework may be insightful. A phylogeny of culturally diverse psy-choactive plant taxa was constructed with their psychotropic effects and affected neu-rotransmitter systems mapped on the phylogeny.

The phylogenetic distribution shows multiple evolutionary origins of psychoactive families. The plant families Myristicaceae (e.g., nutmeg), Papaveraceae (opium poppy), Cactaceae (peyote), Convolvulaceae (morning glory), Solanaceae (tobacco), Lamiaceae (mints), Apocynaceae (dogbane) have a disproportionate number of psychoactive genera with various indigenous groups using geographically disparate members of these plant families for the same psychoactive effect, an example of cultural convergence. Pharmacological traits related to hallucinogenic and sedative potential are phylogenetically conserved within families. **(Sullivan RJ & al.,2002).**

Unrelated families exercising similar psychological effects also modify similar neurotransmitter systems (i.e. mechanical affinity). However, pharmaceutical The mechanisms of stimulant effects differed even within households indicating that stimulant chemicals may be more evolutionarily toxic than those associated with Hallucinogenic and soothing effects**.(Merlin MD. 2003).** Similar psychoactive chemicals may also exist in ethnically unrelated strains, indicating a convergent evolution or Differential genetic regulation of the common metabolic pathway. Recent studies have shown that genetic

analysis of traditionally used psychoactive plants indicates multiple ethnic origins and man's widespread dependence on these plants, stimulating pharmacological investigation of their potential as modern treatments for various neurological disorders.



Chapter Tow

1.Introduction

It is evident that phytotherapy during the last 20 years has gained significance in drug therapy; in spite of this concerns have been voiced by practitioners of conventional medicine with respect to the use of plant derived, "herbal" medicines**.(Ferreira.T & al.,2014).**On balance, most properly cultivated and prepared herbal medicines are usually free of side effects, while synthetic drugs frequently produce undesirable adverse effects

But the addition of herbal medicine in its therapeutic approach allows it to considerably expand its field of efficacy and consequently its field of activity, not only in the context of all functional conditions, but also in most organic diseases, in isolated prescription or, in the latter cases, if necessary in association with allopathy**.(Heinrich, M. & al., 2017).**

We can affirm that herbal medicine can and should be an important part of our daily therapeutic arsenal, without being considered a marginal or outdated practice**.(Capasso, F& al.,2003).** Of course, the medical herbalist does not forbid himself to prescribe any synthetic molecule which he deems useful and necessary for the healing of his patient, But he will only do so wisely and wisely, evaluating the best benefit/risk ratio, and above all by giving thought to his actions: with equal effectiveness, the physiotherapist prefers to choose herbal medicine and/or aromatherapy rather than a treatment using synthetic molecules. The corollary of this preference is that it does not claim to cure everything with plants: at any time, it can supplement or replace its “phytomedicines” (standardized plant products consisting of complex mixtures of one or more plants) treatment with other more conventional prescription if necessary.

2. Phytotherapy

In this respect phytotherapy must be seen as an integration of pharmacognosy, pharmacology and pathology that enables students, physicians and practitioners to understand why, when and how herbal medicines can be used to treat diseases. **(Wichtl M & al.,2003).**The word "herbal medicine" consists etymologically of two Greek roots: phuton and therapy, which mean respectively "plant" and "treatment".

Physiotherapy can therefore be defined as an allopathic discipline intended to prevent and treat certain functional disorders and/or pathological conditions by means of plants, parts of

plants or herbal preparations, whether they are consumed or used externally**.(Porter, S. 2013).**

Since 1987, herbal medicine has been fully recognized by the Academy of Medicine.It is important not to confuse this discipline with the plant medicine, which, in turn, refers to all the substances used to treat plants, namely pesticides, fungicides, herbicides, or insecticides**.(Jamet J.-F. juin 1988.)**

There are two types of herbal therapies:

- First is traditional herbal medicine. It is an alternative therapy that is intended to treat the symptoms of a condition**.(Woerdenbag, H. J & al., 2014).** Its origins can sometimes be very old and it is based on the use of plants according to the virtues discovered empirically.. The relevant information is first-line, specific to the pharmaceutical council**.(Leclerc H.1999).** They concern in particular seasonal pathologies from mild psychosomatic disorders with Hepatobiliary symptoms, as well as digestive or dermatological disorders. Examples include Milk Thistle (Silybum marianum L.).
- The second form is clinical herbal medicine : It is a field medicine in which the patient goes before the disease**.(Chen, X. W & al.,2011).** A comprehensive approach to the patient and his environment is required to determine treatment, as well as a comprehensive clinical examination. Its mode of action is based on a long-term treatment acting on the Neuro-vegetative system.

3.Objectives of the association of botany with the field of medicine

This time the indications are related to a complementary therapy. They complement or reinforce the effectiveness of a classical allopathic treatment for acute pathologies of moderate importance (influenza infection, pathologies E.N.T , etc.). We're gonna focus on the side effects. One example is the use in a vagotonic of lavender (Lavandula angustifolia Mill.) for internal use for its anti-stress effects, calming, and for its actions against muscle cramps, as well as against sleep disorders.

The main asset of herbal medicine is the exceptional tolerance of medicinal plants, if they are chosen carefully respecting the indications, contraindications and taking into account

possible interactions**.(Vickers, A & al.,1999).** This advantage helps to avoid side effects, rebound problems, negative feedback and addiction so frequently encountered with synthetic drugs Nowadays, Herbal medicine is based on scientific advances and researches of active extracts of plants. Once identified, these are standardized. This practice leads to phytomedicines and according to the regulations in force in the country, the circulation of the latter is subject to the marketing authorisation. We are talking about Pharmacognosia or pharmaceutical biology. Modern herbal medicine therefore finds its justification in pharmacognosia, a multidisciplinary aspect of the knowledge of the plant and its properties. **(Tyler, V. E. 1999).**

Finally, it is important to specify that knowing a plant is also to be aware of its limits and its dangers because herbal medicine is in no way an innocuous technique. Its therapeutic use requires a good knowledge of the medical material.

4. the Imortance of Plants in medicines and their branch classes

Herbal medicines meet the definition of "**article L. 5111-1** of the French Public Health Code (P.H.C.) , "Medicinal product" means any substance or composition presented as possessing curative or preventive properties with regard to human or animal diseases, and any product which may be administered to man or animal, to establish a medical diagnosis or to restore, correct or modify their organic functions." The importance of medicinal plants can be recognized by their prominence in the market. Several analyses in recent years have revealed that about 30% of all prescriptions issued in Europe, the United States of America and Canada contain herb, purified extract or active ingredient (or small part) derived from herbs. In other countries of the world herbs can be present in 70-90% of prescriptions.

As for the term "herbal medicinal products", Module 3 of the Order of 23 April 2004 (O.J. of 20 May 2004); gives an official definition: "For the purposes of this Annex, the terms "plant substances" and "herbal preparations""shall be considered equivalent to the terms "vegetable drugs" and "vegetable drug preparations" as defined in the European "Pharmacopoeia."

We can therefore more commonly define herbal medicines : as medicines whose active ingredients are exclusively vegetable drugs and/or vegetable drug(s) preparations Their components with known therapeutic effects are substances or groups of substances, defined

chemically, whose contribution to the therapeutic effect of a plant drug or preparation is known**. (Vickers, A & al.,1999).**

Table 02 :. List of all names of patented drugs and names of chemicals/drugs from plant names and herbal drugs classified in many States**.(Leslie Taylor & al.,2000).**

Drug/Chemical	Action/Clinical Use	Plant Source
Acetyldigoxin	Cardiotonic	Digitalis lanata
Adoniside	Cardiotonic	Adonis vernalis
Aescin	Anti-inflammatory	Aesculus hippocastanum
Aesculetin	Anti-dysentery	Frazinus rhychophylla
Agrimophol	Anthelmintic	Agrimonia supatoria
Ajmalicine	Circulatory Disorders	Rauvolfia sepentina
Allantoin	Vulnerary	Several plants
Allyl isothiocyanate	Rubefacient	Brassica nigra
Anabesine	Skeletal muscle relaxant	Anabasis sphylla
Andrographolide	Baccillary dysentery	Andrographis paniculata
Anisodamine	Anticholinergic	Anisodus tanguticus
Anisodine	Anticholinergic	Anisodus tanguticus
Arecoline	Anthelmintic	Areca catechu
Asiaticoside	Vulnerary	Centella asiatica
Atropine	Anticholinergic	Atropa belladonna
Benzyl benzoate	Scabicide	Several plants
Berberine	Bacillary dysentery	Berberis vulgaris

Follow Table 2

Bergenin	Antitussive	Ardisia japonica
Betulinic acid	Anticancerous	Betula alba
Borneol	Antipyretic, analgesic, antiinflammatory	Several plants
Bromelain	Anti-inflammatory, proteolytic	Ananas comosus
Caffeine	CNS stimulant	Camellia sinensis

Camphor	Rubefacient	Cinnamomum camphora
Camptothecin	Anticancerous	Camptotheca acuminata
(+)-Catechin	Haemostatic	Potentilla fragarioides
Chymopapain	Proteolytic, mucolytic	Carica papaya
Cissampeline	Skeletal muscle relaxant	Cissampelos pareira
Cocaine	Local anaesthetic	Erythroxylum coca
Codeine	Analgesic, antitussive	Papaver somniferum
Colchiceine amide	Antitumor agent	Colchicum autumnale
Colchicine	Antitumor agent, anti-gout	Colchicum autumnale
Convallatoxin	Cardiotonic	Convallaria majalis
Curcumin	Choleretic	Curcuma longa
Cynarin	Choleretic	Cynara scolymus
Danthron	Laxative	Cassia species
Demecolcine	Antitumor agent	Colchicum autumnale
Deserpidine	Antihypertensive, tranquillizer	Rauvolfia canescens
Deslanoside	Cardiotonic	Digitalis lanata
L-Dopa	Anti-parkinsonism	Mucuna sp
Digitalin	Cardiotonic	Digitalis purpurea
Digitoxin	Cardiotonic	Digitalis purpurea
Digoxin	Cardiotonic	Digitalis purpurea
Emetine	Amoebicide, emetic	Cephaelis ipecacuanha
Ephedrine	Sympathomimetic, antihistamine	Ephedra sinica
Etoposide	Antitumor agent	Podophyllum peltatum
Galanthamine	Cholinesterase inhibitor	Lycoris squamigera
Gitalin	Cardiotonic	Digitalis purpurea
Glaucarubin	Amoebicide	Simarouba glauca
Glaucine	Antitussive	Glaucium flavum
Glasiovine	Antidepressant	Octea glaziovii
Glycyrrhizin	Sweetener, Addison's disease	Glycyrrhiza glabra

Gossypol	Male contraceptive	Gossypium species
Hemsleyadin	Bacillary dysentery	Hemsleya amabilis
Hesperidin	Capillary fragility	Citrus species
Hydrastine	Hemostatic, astringent	Hydrastis canadensis
Hyoscyamine	Anticholinergic	Hyoscyamus niger
Irinotecan	Anticancer, antitumor agent	Camptotheca acuminata
Kaibic acud	Ascaricide	Digenea simplex
Kawain	Tranquillizer	Piper methysticum
Kheltin	Bronchodilator	Ammi visaga
Lanatosides A, B, C	Cardiotonic	Digitalis lanata
Lapachol	Anticancer, antitumor	Tabebuia sp.
a-Lobeline	Smoking deterrant, respiratory stimulant	Lobelia inflata
Menthol	Rubefacient	Mentha species
Methyl salicylate	Rubefacient	Gaultheria procumbens
Monocrotaline	Antitumor agent (topical)	Crotalaria sessiliflora
Morphine	Analgesic	Papaver somniferum
Neoandrographolide	Dysentery	Andrographis paniculata
Nicotine	Insecticide	Nicotiana tabacum
Nordihydroguaiaretic acid	Antioxidant	Larrea divaricata
Noscapine	Antitussive	Papaver somniferum
Ouabain	Cardiotonic	Strophanthus gratus
Pachycarpine	Oxytocic	Sophora pschycarpa
Palmatine	Antipyretic, detoxicant	Coptis japonica
Papain	Proteolytic, mucolytic	Carica papaya
Papavarine	Smooth muscle relaxant	Papaver somniferum
Phyllodulcin	Sweetner	Hydrangea macrophylla
Physostigmine	Cholinesterase Inhibitor	Physostigma venenosum

Picrotoxin	Analeptic	Anamirta cocculus
Pilocarpine	Parasympathomimetic	Pilocarpus jaborandi
Pinitol	Expectorant	Several plants
Podophyllotoxin	Antitumor anticancer agent	Podophyllum peltatum
Protoveratrines A, B	Antihypertensives	Veratrum album
Pseudoephredrine*	Sympathomimetic	Ephedra sinica
Pseudoephedrine, nor-	Sympathomimetic	Ephedra sinica
Quinidine	Antiarrhythmic	Cinchona ledgeriana
Quinine	Antimalarial, antipyretic	Cinchona ledgeriana
Qulsqualic acid	Anthelmintic	Quisqualis indica
Rescinnamine	Antihypertensive, tranquillizer	Rauvolfia serpentina
Reserpine	Antihypertensive, tranquillizer	Rauvolfia serpentina
Rhomitoxin	Antihypertensive, tranquillizer	Rhododendron molle
Rorifone	Antitussive	Rorippa indica
Rotenone	Piscicide, Insecticide	Lonchocarpus nicou
Rotundine	Analagesic, sedative, traquillizer	Stephania sinica
Rutin	Capillary fragility	Citrus species
Salicin	Analgesic	Salix alba
Sanguinarine	Dental plaque inhibitor	Sanguinaria canadensis
Santonin	Ascaricide	Artemisia maritma
Scillarin A	Cardiotonic	Urginea maritima
Scopolamine	Sedative	Datura species
Sennosides A, B	Laxative	Cassia species
Silymarin	Antihepatotoxic	Silybum marianum
Sparteine	Oxytocic	Cytisus scoparius
Stevioside	Sweetner	Stevia rebaudiana
Strychnine	CNS stimulant	Strychnos nux-vomica
Taxol	Antitumor agent	Taxus brevifolia
Teniposide	Antitumor agent	Podophyllum peltatum
Tetrahydrocannabinol (THC)	Antiemetic, decrease occular Tension	Cannabis sativa

Tetrahydropalmatine	Analgesic, sedative, traquillizer	Corydalis ambigua
Tetrandrine	Antihypertensive	Stephania tetrandra
Theobromine	Diuretic, vasodilator	Theobroma cacao
Theophylline	Diuretic, brochodilator	Theobroma cacao and others
Thymol	Antifungal (topical)	Thymus vulgaris
Topotecan	Antitumor, anticancer agent	Camptotheca acuminata
Trichosanthin	Abortifacient	Trichosanthes kirilowii
Tubocurarine	Skeletal muscle relaxant	Chondodendron tomentosum
Valapotriates	Sedative	Valeriana officinalis
Vasicine	Cerebral stimulant	Vinca minor
Vinblastine	Antitumor, Antileukemic agent	Catharanthus roseus
Vincristine	Antitumor, Antileukemic agent	Catharanthus roseus
Yohimbine	Aphrodisiac	Pausinystalia yohimbe
Yuanhuacine	Abortifacient	Daphne genkwa
Yuanhuadine	Abortifacient	Daphne genkwa

5. The rool of The herbal medicin in the scientific research

The interest in the pharmaceutical industry of plants in the pharmaceutical industry is largely due to the emergence of high-productivity screening as a major way to find new drugs with new working methods.**(Acimovic M & al., 2021).**Access to a variety of inputs and effectiveness, perhaps a very harsh strategy for the follow-up of initial activities, is crucial to this programme's success. These factors, in turn, depend on establishing effective cooperative relationships between factory suppliers and those seriously involved in drug discovery. Creating a plant research initiative creates practical challenges. However, overcoming obstacles can build a program that has a significant impact, not only in high-productivity screening, but also in alternative approaches to drug discovery.

In fact, more than half 25 The world's best-selling pharmaceuticals for 1991 owe their origin to one of a range of natural source substances **(Sneader,W., 1985); (Chalier, R & al.,1962)**. Nature's ability to manufacture highly diverse chemicals, some of which possess remarkable selective biological activities, is well known to today's scientists involved in drug discovery. Over the past decade, high-productivity screening against mechanically pure physiological targets has come to the forefront in the search for new chemical entities.The current vogue in the pharmaceutical industry for highly automated, sensitive target screening as a major strategy in drug discovery, has prompted renewed interest in natural product sources of biologically active compounds. **(Bonilla D.A & al.,2021).**

In 2020, for the 12th consecutive year, sales increased in both NBJ market channels. The strongest growth in 2020 was in the mass market channel, which increased by 25.1% from 2019 and totaled $2.131 billion in 2020. This is more than double sales growth of 9.4% in this channel from 2018 to 2019. Direct sales of herbal supplements, which include online sales, increased by 23.7% in 2020, more than double the 11.5% growth seen in 2019. Sales in NBJ's natural, health and specialist channel increased by 1.6% in 2020 and totaled $2.950 billion. Despite moderate sales growth in the natural channel of NBJ, total sales in this channel were higher than in the mass market channel since at least 2005, when HerbalGram began to include sales data for the three market channels of NBJ. In recent years, however, the difference in total sales between these two channels has decreased. **(Tyler Smith, 2021).**This is what the following tables offer.

Table03 : Top-Selling Herbal Supplements in 2020 — US Mainstream Multi-Outlet Channel

Source: SPINS (52 weeks ending December 27, 2020).

Rank	Primary Ingredient	Latin Binomial	Total Sales	% Change from 2019
1	Elder berry	*Sambucus nigra* and *S. canadensis*	$275,544,691	**150.3%**
2	Horehound	*Marrubium vulgare*	$137,054,571	**–11.4%**
3	Cranberry	*Vaccinium macrocarpon*	$101,339,826	**12.9%**
4	Turmeric[a]	*Curcuma longa*	$96,971,371	**3.1%**
5	Apple cider vinegar	*Malus* spp.	$79,257,715	**133.8%**
6	Ginger	*Zingiber officinale*	$64,779,632	**39.3%**
7	Echinacea[b]	*Echinacea* spp.	$57,345,210	**36.8%**
8	Garlic	*Allium sativum*	$42,924,030	**12.1%**
9	Fenugreek	*Trigonella foenum-graecum*	$35,148,440	**5.5%**
10	Wheatgrass / Barley	*Triticum aestivum / Hordeum vulgare*	$32,887,254	**9.2%**

	grass			
11	Saw palmetto	*Serenoa repens*	$32,697,628	**5.4%**
12	Ashwagandha	*Withania somnifera*	$31,742,304	**185.2%**
13	Green tea	*Camellia sinensis*	$31,408,078	**–7.9%**
14	Ivy leaf	*Hedera helix*	$29,581,801	**–32.0%**
15	Ginkgo	*Ginkgo biloba*	$28,576,480	**9.7%**
16	Cannabidiol (CBD)	*Cannabis sativa*	$26,551,872	**–30.0%**
17	Black cohosh	*Actaea racemosa*	$24,890,605	**–12.0%**
18	Beta-sitosterol[c]	—	$24,827,065	**52.3%**
19	Red yeast rice[d]	*Oryza sativa*	$24,613,191	**–3.9%**
20	Aloe	*Aloe vera*	$24,403,736	**11.2%**
21	St John's wort	*Hypericum perforatum*	$23,890,515	**0.3%**
22	Flax seed / Flax oil	*Linum usitatissimum*	$22,150,127	**–3.2%**
23	Milk thistle	*Silybum marianum*	$19,823,644	**8.4%**
24	Yohimbe	*Pausinystalia johimbe* syn. *Corynanthe johimbe*	$17,774,381	**–3.7%**
25	Goji berry	*Lycium* spp.	$16,104,457	**15.9%**
26	Valerian	*Valeriana officinalis*	$14,596,855	**–11.2%**
27	Horny goat weed	*Epimedium* spp.	$14,546,366	**1.6%**
28	Bioflavonoid complex[e]	—	$14,137,366	**–4.2%**
29	Beet root	*Beta vulgaris*	$13,945,332	**22.4%**
30	Cinnamon	*Cinnamomum* spp.	$12,339,671	**–18.2%**
31	Senna[f]	*Senna alexandrina*	$12,295,396	**1.0%**
32	Green coffee extract	*Coffea arabica*	$12,263,598	**–21.1%**
33	Plant sterols[g]	—	$11,498,813	**4.3%**
34	Ginseng	*Panax* spp.	$11,200,292	**–11.9%**
35	Chamomile	*Matricaria chamomilla* syn. *M. recutita*	$10,624,567	**30.1%**
36	Garcinia	*Garcinia gummi-gutta*	$10,618,783	**–35.7%**
37	Fennel	*Foeniculum vulgare*	$10,101,137	**9.2%**
38	Maca	*Lepidium meyenii*	$10,075,136	**21.8%**
39	Açaí	*Euterpe oleracea*	$9,835,442	**10.4%**
40	**Rhodiola**	***Rhodiola* spp.**	**$8,433,070**	**–4.3%**

Table 04: Top-Selling Herbal Supplements in 2020 — US Natural Channel Source: **SPINS (52 weeks ending December 27, 2020)**.

Rank	Primary Ingredient	Latin Binomial	Total Sales	%Change from 2019
1	Cannabidiol (CBD)	*Cannabis sativa*	$57,217,025	**–36.9%**
2	Elder berry	*Sambucus nigra* and *S. canadensis*	$54,132,170	**68.2%**

3	Turmeric[a]	*Curcuma longa*	$41,457,226	**–13.7%**
4	Wheatgrass / Barley grass	*Triticum aestivum* / *Hordeum vulgare*	$17,484,031	**–3.0%**
5	Mushrooms (other)	—	$14,986,621	**41.8%**
6	Aloe	*Aloe vera*	$13,784,172	**10.2%**
7	Ashwagandha	*Withania somnifera*	$13,507,542	**–1.2%**
8	Oregano[b]	*Origanum vulgare*	$13,327,549	**43.2%**
9	Echinacea[c]	*Echinacea* spp.	$12,856,524	**23.8%**
10	Flax seed / Flax oil	*Linum usitatissimum*	$11,522,131	**–8.9%**
11	Milk thistle	*Silybum marianum*	$9,152,946	**–8.4%**
12	Echinacea–goldenseal combo	*Echinacea* spp. / *Hydrastis canadensis*	$7,991,152	**27.3%**
13	Saw palmetto	*Serenoa repens*	$7,813,043	**0.8%**
14	Cranberry	*Vaccinium macrocarpon*	$7,715,667	**–3.1%**
15	Garlic	*Allium sativum*	$7,559,525	**10.5%**
16	Maca	*Lepidium meyenii*	$7,105,435	**–5.8%**
17	Valerian	*Valeriana officinalis*	$6,818,876	**0.4%**
18	Nigella	*Nigella sativa*	$6,468,066	**21.6%**
19	Quercetin[d]	—	$6,415,921	**74.1%**
20	Chlorophyll / Chlorella	— / *Chlorella vulgaris*	$5,258,353	**1.6%**
21	Ginkgo	*Ginkgo biloba*	$4,491,630	**–1.8%**
22	Horsetail	*Equisetum* spp.	$4,490,279	**–16.0%**
23	Reishi mushrooms	*Ganoderma lucidum*	$4,480,026	**22.7%**
24	Beet root	*Beta vulgaris*	$3,691,197	**18.0%**
25	Apple cider vinegar	*Malus* spp.	$3,609,865	**97.7%**
26	Olive leaf	*Olea europaea*	$3,580,845	**24.0%**
27	Red yeast rice[e]	*Oryza sativa*	$3,518,993	**–6.5%**
28	Cordyceps mushrooms	*Cordyceps* spp.	$3,482,578	**25.7%**
29	Kava	*Piper methysticum*	$3,414,784	**0.1%**
30	Ginseng	*Panax* spp.	$3,253,793	**–1.2%**
31	Cherry	*Prunus* spp.	$3,245,910	**–11.3%**
32	Ginger	*Zingiber officinale*	$3,197,474	**–4.1%**
33	Resveratrol[f]	—	$3,021,575	**–0.1%**
34	Fenugreek	*Trigonella foenum-graecum*	$2,981,690	**–9.3%**
35	Holy basil	*Ocimum tenuiflorum*	$2,851,773	**–7.9%**
36	Hawthorn	*Crataegus* spp.	$2,816,112	**–3.8%**
37	Stevia	*Stevia rebaudiana*	$2,738,754	**–9.7%**
38	Evening primrose oil	*Oenothera biennis*	$2,738,213	**–8.1%**
39	Nettle	*Urtica dioica*	$2,731,865	**0.6%**

40	**Chaga mushrooms**	***Inonotus obliquus***	**$2,730,506**	**54.9%**

Chapter Three

1. Plant based traditional medicines as sources for novel therapeutic compounds

1.1 Preparations based on vegetable drugs

The plant, living organism, marks its identity with morphological specificities, at the origin of the botanical classification, but also biochemical, linked to novel biosynthetic pathways, representing the interest of the use of medicinal plants**. (Penso, G. 1980).**The medicinal plants belong to the French Pharmacopoeia, which lists them in its various editions, and whose list, revised in 2000, is published in the 10th edition. Official edition, it takes plants from the old list written in 1979 and already published in the 9th edition in January 1993 ."Phytopharmaceutical" is a term used for those medicinal preparations made by extracting botanical products with appropriate solvents to yield extracts, tinctures, or the like. **(Priya, S & al.,.2020).** Ideally, such preparations have been standardized to a chemical marker or pharmacologically active constituents, named "active principles".

"Phytomedicine" is another term proposed by the European Union (EU) and the European Scientific Cooperative for Phytotherapy (ESCOP)to indicate phytopharmaceuticals**. (Robard, I;2004).** According to the 10th edition of the French Pharmacopoeia, medicinal plants "are plant drugs within the meaning of the European Pharmacopoeia, at least some of which have medicinal properties".These medicinal plants can also have food, condiment or hygienic uses. In other words, we can say that a medicinal plant is a plant of which one of the organs, for example the leaf or the bark, has healing properties when used at a certain dosage and in a precise manner.

In the Public Health Code, there is no legal definition of a medicinal plant in the legal sense. It is a plant, not mentioned as a medicinal, which is sold over the counter by pharmacists. The medicinal plants belong to the French Pharmacopoeia, which lists them in its various editions, and whose list, revised in 2000, is published in the 10th edition. Official edition, it takes plants from the old list written in 1979 and already published in the 9th edition in January 1993 . **(Grenand P & al.,1987).**

Raw medicines : called medieval "minimalists", represent dried, fresh herbs or a prefix from which chemical pure compounds can be isolated. "Depending on their specific use,

therefore, medicinal plants are those used for medical purposes. They must contain active principles that exert a pharmacological effect. And in figure 03 we see whaw a they a crude drug preparation retains most or all of the active and inactive compounds contained in the natural source from which it was derived. After a pure drug compound (e.g., morphine) is extracted from a crude drug preparation (in this case, opium), it is possible to manufacture pharmaceutic preparations that are suitable for administration of a particular dose to the patient.

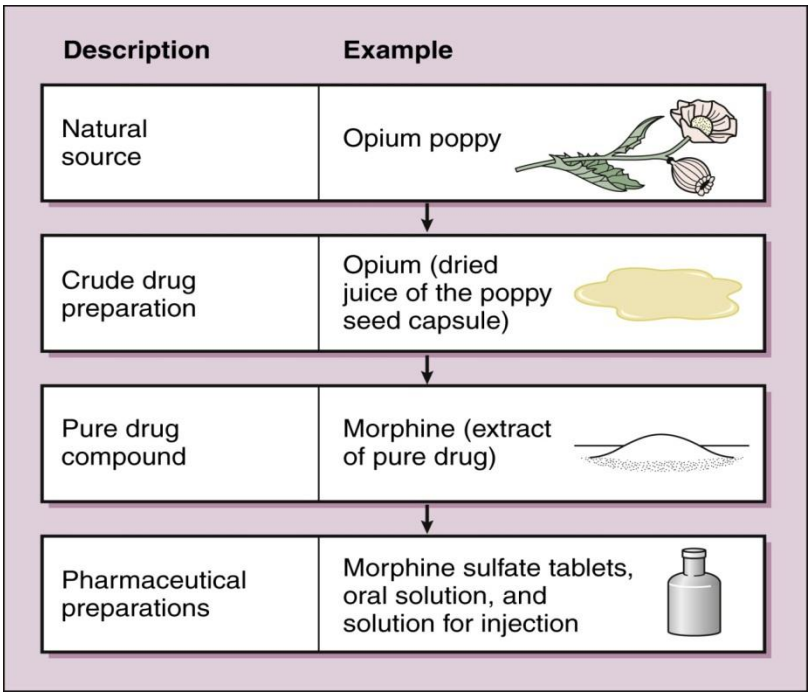


Figure 03 : Image represent 2 Types of drug preparations**.(Francesco Capasso & Al.,2003).**

1.2. Legal definition of a medicinal plant

The use of medicinal plants is part of the wider development of traditional or non-conventional medicines, according to the official term of the European Parliament. The World Health Organization (WHO) defines traditional medicine as a medicine comprising "various practices, approaches, health knowledge and beliefs incorporating herbal, animal and/or mineral-based medicines, spiritual treatments, manual techniques and exercises, applied alone or in combination to maintain well-being and treat, diagnose or prevent the disease." In its 2002-2005 programme, the WHO affirms the need to integrate traditional medicines into health systems in developing countries as well as in developed countries. The growing development of the global market for traditional medicines based on According to the WHO, plants are estimated at $60,000 million. In parallel with this phenomenon of the development of unconventional medicines, the citizen aspires to take control of his own body and his health. As a patient, the individual becomes a user of health, a consumer of health care, a player in his own health**. (Bilia, A. R & al.,2021).**

A medicinal plant has no legal definition**. (Ajazuddin, S. S. 2012)** .It is the case law that states that a plant is medicinal. For this it must be registered in the Pharmacopoeia and have an exclusively medicinal use. Only that part of the plant listed in the Pharmacopoeia belongs to the pharmaceutical monopoly.

The List of Medicinal Plants is an integral part of the French Pharmacopoeia Tenth edition . It is presented in table form and is structured in 2 parts:

1.2.1 List A : "Medicinal plants traditionally".

1.2.2 List B: "Medicinal plants traditionally": used in the state or in the form of preparation whose potential adverse effects are greater than the expected therapeutic benefit".

1.3. Vegetable drug formulations

Herbal therapy is the use of plants to treat or prevent diseases. Flowering leaves, flowers and tops, roots or whole plants are used. Can be used spontaneous or cultivated plants, but the regulatory conditions for clean cultivation must be Required. The use of plants is by internal ingestion or external application in the form of herbal teas, Capsules, alcohols and tinctures,

of extracts. Plants have a number of constituents that are potentiating and harmonizing,constituting the totum of the plant, in contrast to the allo-therapy which concentrates in significant quantity a only a few molecule .The ways in which plants are used are different depending on how they are prescribed: internally (oral absorption, gargling, mouth rinse) or externally (poultice, lotion, gargling, mouth rinse, bath, natural injection cavities, fumigation).

1.4. Totum

" The whole is greater than the sum of its parts " is the fundamental principle endorsed by Ibn Sina, doctor and philosopher, better known by the name Avicenna (980-1037, and the concept of the plant totum fits in with this. With the plant totum, the laws of mathematics are challenged, and 1+1 > 2" **.(Marder M & al., 2003).**

The notion of totemical vegetation is unique to medicinal plants. It can be defined as all plant ingredients, as with all natural substances found in the plant. Vegetable totem can contain several hundred different chemical ingredients.Plants contain various active compounds, which each play a different role and act in harmony to achieve a given activity. This specific mode of action, which involves several substances at once, is called synergy of action.

2. Parts to be used, labels, purchase and preserve medicines

2.1 Nomenclature

The names of the plant drugs are most appropriately expressed in pharmaceutical Latin. The Latin names generally indicate the genus and/or species of the plant, followed by the Latin name of the part of the plant from which the drug derives. So when referring to the whole plant, the botanical name is followed by the Latin name herba (Malva sylvestrisherba). When referring to the root, rhizome, bulb, tuber, caulis, wood, bark or leaf, these names are followed by radix (Glycirrhiza glabra radix), rhizome (Rheum palmatum rhizome), bulbus (Urginea maritime bulbus), tuber (Colchicum autumnale tuber), caulis (Equisetum arvense caulis), lignum (Quassia amara lignum), cortex (Cinchona succirubracortex), folium (Digitalis purpurea folium). When referring to the fruit .the term used is fructus (Vaccinium vitis

fructus), epicarpurn (Citrus aurantium epicarpum), or pulpa (Tamarindus indica pulpa). For seeds the term semen (Linum usitatissimum semen) and for sprouts the term thallus (Cetraria islandica thallus) is used. **(Francesco Capasso& al., 2003).**

2.2. Preparation of raw drugs

The crude drugs sold in industrialised countries are mostly imported from Eastern Europe and developing countries. In these countries the personnel employed in the plant picking and drug separation processes may lack proper qualifications. **(Zhang, J & al., 2012).** This and the fact that local names are used, not scientific ones, create confusion among the same personnel.Consequently there is the risk of finding one drug instead of another on the market; For this reason, plus the fact that today drugs are sold in rather small pieces or even in powder form, it is absolutely necessary to issue the following information in order to guarantee the soundness and quality of any botanical drug.

- The place of origin of the plant which provides the drug (economic and environmental factors influencing the drug active principle content).
- The nature of the plant itself, wild or cultivated (exogenous, endogenous and biotic factors significantly modifying the drug active principle content).

3. Extraction of raw material from plant origin

Herbal medicines are obtained from either wild or cultivated plants with economic factors usually determining the choice**.(Hodge, W. H. 1955)**. It may be more advisable to obtain the drug from wild plants which are particularly common, For herbal medicines, the raw materials can be of various types and come in different forms such as vegetable drugs, extracts, or essential oils, a raw material is a product obtained in its condition before any processing. It is therefore intended to be modified to reach the finished product ready for use.In herbal medicine, in order to ensure optimal efficacy of the product as well as good adherence of the treatment on the part of the patient, the raw materials must meet an extremely complete and rigorous specification. This corresponds to the regulatory and ethical requirements of the herbal medicine, which are all the more demanding when the molecules are of natural origin, and not of synthesis. **(Popov, V. G. & al., 2017).**

First of all a selection of fresh plants perfectly identified botanically is essential. Organic farming or reasoned agriculture is preferable. Next, the use of a full retrieval process is desired.Indeed, it guarantees respect for the integrity and completeness of the active principles contained in the original plant in order to restore its molecular composition.In addition, numerous controls will be carried out, in order to know the product as far as possible. For this a thorough analysis of the composition is necessary, as well as a search for contaminants even in minute quantities. These can be microbiological, chemical or radioactive.

Finally, the finished product must be in a clinical form well accepted by the patient and with exemplary compliance with the regulations.

4. Active parts and classifications

parts of the plant used for medical purposes plants contain a raw drug in the form of powder material from the part of the plant that has been identified for biological activity, or as various aquatic, alcoholic or other extracts. The factory part used for the preparation should be identified. Producing medicinal plants.Covers two originals simultaneously. First, the spontaneous plants called "wild" or "picking", then the plants planted **.(Bézanger-Beauquesne L & al., 1986.) .**

4.1. Volunteer plants

They have been the only ones used in the past and continue to account for a significant percentage of the European market.Their distribution depends on the soil and especially on the climate. We can list the main factors influencing their development below **(Perrot E & al.,1974) .**

4.1.1. Soil

Its effect on plant growth is defined by what are called edaphic conditions.Seedlings develop effectively and naturally in the soil that is most favourable to them. For example, Broom-to-Broom (Cytisus scoparius L.) or Foxglove (Digitalis purpurea L.) will be spontaneously encountered in the acid siliceous soils of the Vosges. Lavender (Lavandula angustifolia Mill.) and many other Lamiaceae prefer limestone soils, such as Provence in the south-east of France.

4.1.2. Climate

Climatic conditions play an important role in the distribution of medicinal plants. It is in fact a set of several factors that constitute the climate and these will therefore allow a more or less advanced development of the young plant**. (Mehdipoor, H. 2015).**

First of all, the temperature is involved; it is closely related to latitude, but also altitude and distance from the sea.

Second, humidity and insulation are also part of the climate and will play their role on the surrounding vegetation.They can also be modified by wind conditions. The average temperature, but also the temperature differences, is very important for the distribution of medicinal plants.

The intensity of light required for the good development of plants is variable. Here again several categories of plants stand out. Heliophilic individuals are those who love the sun. In contrast, there are heliophobe or parasophilic subjects. These, of course, prefer undergrowth. Naturally, some plants thrive in conditions far from their natural habitat.In this case their degree of development is modified, as well as their content, of active ingredients and thus by their physiological activity.

Finally, the medicinal value of spontaneous plants is very uneven in the territory as it varies depending on origin, terrain and growing conditions.

4.2. Crop plants

Rural and tribal populations living in remote or forested areas remain Largely on local systems of medicine and agriculture. So far, there are many tribes that rely on Crop plants, especially from India's northeastern tribes, such as Lear, Maker, Carpice, Merice, Khase, Jentai, Garo, Monbas, Nishi, Abatani, Riang, etc. **(Dutta, B. K & al.,2005).**

A wide range of plants with plant ethnicity value have been reported against some very important diseases, given the importance that must Conserving the resources of crop plants and wild relatives of crop plants is vital for the future breeding programme. This aspect of the study should also be given the deserving effect and, therefore, research work should continue

on the economically important plants used by the northeastern tribe so that These plants can be preserved and known before they are lost forever.

5 . Plant parts and his active components

The desired bodies, They are many natures and very varied.The list of organs sought for therapy can extend from one end of the plant to the other, and throughout the season. Indeed, the underground organs, which regroup the roots, rhizomes and tubers, will be harvested outside the period of full vegetation so that they are richer in active constituents . Therefore, fall or winter is the preferred vegetative rest period for plants **(Leclerc H., 1999).** .

In order to reduce expenses, many herbal medicines tend to be marketed as powders or cut into small pieces, depending on the active ingredients in their composition that form in the following axes **(Francesco Capasso & al., 2003)**.

1) Roots: are the underground parts of the plant and serve to anchor it. They are free of buds, leaves, knots and internists. In the dried state they are of a cylindrical or conical form, with a wrinkled surface, free of knots or lichen traces .

2) Rhizomes : are cylindrical-shaped underground stems, more or less swollen and fleshy, with small scales from which leaf, root and bud systems are developed. In the dried state they have an elongated, cylindrical form with marks and scarring from leaves, roots and shoots.

3) Tubers: are fusiform or spheroidal form underground organs (stems, rhizomes, roots and leaves). In dried state they have a spheroidal form showing the marks of shoots and roots.

4) Bulbs: are spheroidal underground organs with short stems at the counter, which are covered by numerous and rather fleshy leaves (scales). The isolated scales (which are in the form of lamellae) or the whole bulb with roots or the remains of these can be used for the drug.

5) The cortex: is the external part of the stems, branches and roots. When dried, it is in flat pieces, rugose and rough, cylindrical or grooved. The wood is the part of the stem

between (and including) the cambium and Medulla. When dried, it is hard with a stratified structure .

6) Herbs : are drugs which are composed of the entire herbaceous plant.The dried parts used are the caulis, leaves and flowers.

7) Flowering : tops are the terminal flowers. When dried the parts used are the leaves and attimes the fruit .

8) The leaves : are appendices and extensions of stems and have a respiratory function. They are composed of a main stem (petiole) and a leaf (lamina). Those without a main stem are called sessiles. Dried leaves are distinguished from one another by the form of the lamina (oval, lanceolate etc.), by the form of the lamina margin (serrated, crenated etc.), by the form of the nervature (single or parallel veins etc.) and by the presence or lack of a main stem.

9) Flowers : are the reproductive organs. They can be with or without a peduncle, in the latter case sessile; they can be isolated flowers or in a clump (raceme, spike, corymb, etc.).In dried state the latter are distinguished by the easiness with which they are crushed .

10) Fruits : are ovary transformations after fertilization and following ripening. Their function is to propagate the species. In dried state the parts that can be used are the skin or epicarp, the fleshy part or mesocarp, the peduncle or main stem or the whole fruit.

11) The seeds: are transformed ovules after fertilization. Each seed consists of a husk and a kernel. In dried state they are hard, of different shapes, coloured and in some cases covered with fine hair. They can be used with or without the husk removed (for example, ricinus seeds)

12) Sprouts : are undifferentiated lower plant bodies (thallophytes), not as cormophytes, roots, stems, and leaves, etc. Their cellular tissue is always morphologically homogeneous. In dried state they are filiform or membraneous branches (algae,lichen) or spungy bodies differing in volume and appearance (fungus).

13) Galls (cecids) : are caused by parasites which establish themselves in a plant organ stimulating abnormal development. These pathological for mations are constant in form, thus

permitting description. When dried they are globular bodies, hard, heavy with a small base main stem and with roundish surface projections.

6. Active principles

The term "active principle" refers to the essential chemical that stimulates pharmaceutical activity. Plant organisms, although different in shape, regulation and environmental adaptability, use a fairly limited number of substances for their biochemical processes (carbohydrates, fats, proteins, nuclear acids, co-enzymes and vitamins).

Plants are often able to manufacture a large variety of organic compounds, the importance of which is only apparent in some cases - the essential oils of conifers are useful in that resin solvents act as protective wounds. Active principles form mainly during the plant's growth period when metabolic transformation is at its greatest**. (Alupului, A & al., 2012).**

Primary cellular ingredients (proteins, fat, multiple sugars), intermediate metabolites (organic acids) and sub-cellular components (alkaloids, glycosides, flavonoids, saponins, tannins, cells, etc.). The total plant therefore forms a complex and coherent set of ingredients for one part of the plant, producing a correlative value called synergy that provides a different or additional effect compared to its components taken in isolation. **(Farnsworth, N & al.,1985).**

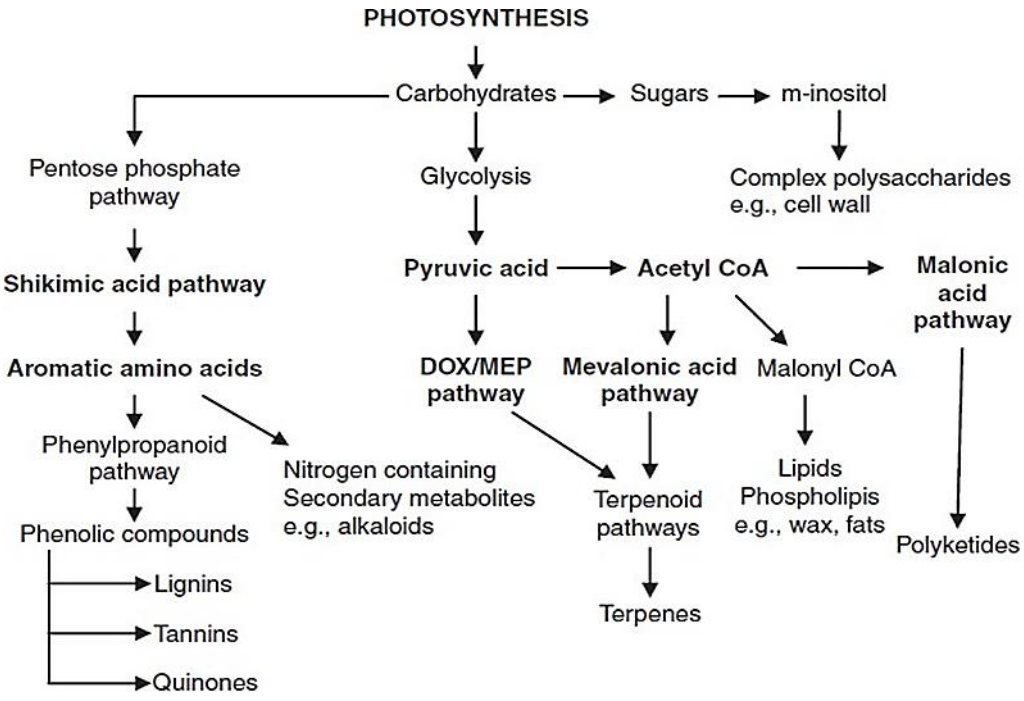


Figure 04: . General scheme of biosynthetic pathways and precursors for the major classes of secondary metabolites. **(Ghasemzadeh, A & al.,2011).**

6.1. Alkaloids

Alkaloids form a very large family of nitrogen-containing substances present in the plant kingdom. Some alkaloids are strong poisons, for example, curare, which has the ability to paralyze the nervous system. Alkaloids are considered to be an insecticide defense means in plants. Some alkaloids, for example nicotine, play a role in enzymatic oxidation-reduction processes. **(Waller, G. R & al.,1978).**

The alkaloid-producing plants are dicotyledons, and to a lesser extent monocotyledons and cryptogamas. Generally, a plant contains several alkaloids. The alkaloid content depends on the age of the plant, region, climate and season. Algae and bryophytes do not produce alkaloids. They are rare in mushrooms (ergotamine), in pteridophytes (nicotine in Equisetum, coniine in Lycopodium spores) and in gymnosperms (ephedrine). In the angiosperms, some families are reputed by their high contents in alkaloids: Solanaceae (solanine, nicotine, hyoscyamine, atropine), Rubiaceae (caffeine, quinine), and Papaveraceae (morphine, papaverine, codeine, narceine, etc.). **(Hartmann, T & al.,2000)**. The most important

alkaloids are: coniine, nicotine, tropane, atropine, cocaine, quinine, papaverine, morphine, codeine, strychnine, caffeine, and others .

They are highly heterogeneous from a chemical point of view as well as for the pharmacological action they possess. It can generally be said that these basic molecules, apart from nitrogen, contain carbon and oxygen. Oxygenated alkaloids are solid, crystallizable and not very volatile. Those without oxygen can take the form of liquid, oily liquid or crystallizable solids. Most of these are colorless, little soluble in water but soluble in organic solvents.

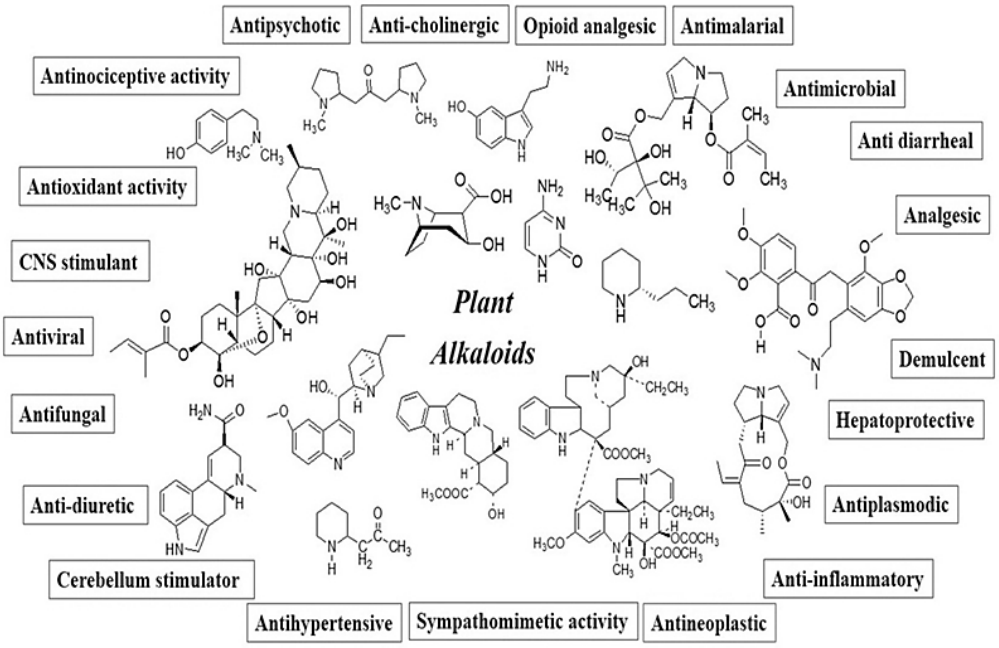


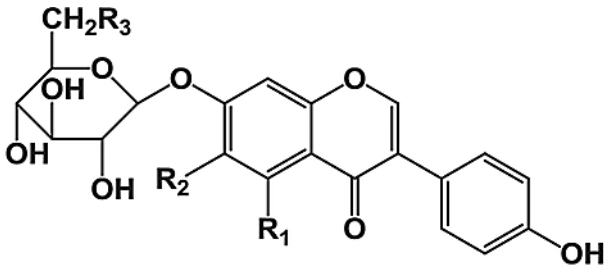
Figure 05 : The role of alkaloids in the pharmaceutical industry and its installation.

(Francesco Capasso & al.,2003)

6.2. Glycosides

These are complex organic substances mainly present in the plant world. They consist of two parts, of which one is a sugar (saccharide) molecule and the other an aglycone. The sugar moiety can be joined to the aglycone in various ways. The most common bridging atom is oxygen (a-glycoside), but it can also be sulphur (S-glycoside), nitrogen (N-glycoside) or carbon (C-glycoside). They are usually solid, sufficiently soluble in water and alcohol but little soluble in ether.

The glycosidic link is resistant to alkaline hydrolysis but is easily separated by enzymatic action of glycosidases or by dilute mineral acids. From a pharmacological point of view glycosides are a heterogenous family. **(Bartnik, M & al., 2017)**.Naturally-occurring glycosides are present in significant amounts in medicinal plants. Several of these glycosides possess anticancer activity. Glycosides extracted from medicinal plants have been recognized and employed as alternative drugs in treating different cancers. In this review, we demonstrate that natural glycosides provide a wide range of preventive and therapeutic options against different types of cancer either alone or in combination with other chemotherapeutic drugs .



Name	R_1	R_2	R_3
Daidzin	H	H	H
Acetydaidzin	H	H	$COCH_3$
Malonyldaidzin	H	H	$COCH_2COOH$
Genistin	OH	H	H
Acetylgenistin	OH	H	$COCH_3$
Malonylgenistin	OH	H	$COCH_2COOH$
Glycitin	H	OCH_3	H
Acetylglycitin	H	OCH_3	$COCH_3$
Malonylglycitin	H	OCH_3	$COCH_2COOH$

Figure 06: Structure-of-main-isoflavone-glycosides **(https://www.researchgate.net/figure/Structure-of-main-isoflavone-glycosides_fig3_319388397)**

6.3. Flavonoids

Flavonoids are phenolic compounds found in land plants like bryophytes (hornworts, liverworts, mosses) and vascular plants (ferns, gymnosperms, angiosperms). They are synthesized in the cytoplasm of the plant cell and then accumulate in vacuoles that fuse with the central vacuole of epidermis and cortex cells. Flavonoids have a defensive function

against insects, fungi and viruses, as well as against invading invertebrates, they are yellow compounds, very common in nature. Citrus fruits, such as Citrus medica (lemons), Citrus aurantium (oranges) in their bitter and sweet varieties, and some wild fruits like Rosa canina are very rich in these flavonoids. Chemically they are derivatives of flavone (2-phenyl-benzo-y-pyrone) and some (named isoflavonoids) from isoflavone (3-phenyl-benzo-y-pyrone); they are usually soluble in water and boiling alcohol. Many flavonoids are the aglycone of natural glycosides that are formed by the bond of one or more sugars in position 7 or position 3. **(Iwashina, T. 2000).**

The biological action of flavonoids is due to their ability to complex soluble and extracellular proteins and to bind to the bacterial cell wall. It has been shown that several lipophilic flavonoids may disrupt cell membranes Chemically related to flavonoids are flavonolignans, anthocyanins and proanthocyanidins. Flavonolignans (or flavolignans) are hybrid lignans derived from the flavonoid taxifolin (2,3-dihydroquercetin) and coniferyl alcohol. Silybin is a flavonolignan isolated from the fruit of Sylibum marianum (milk thistle). **(Samanta, A & al.,2011).**

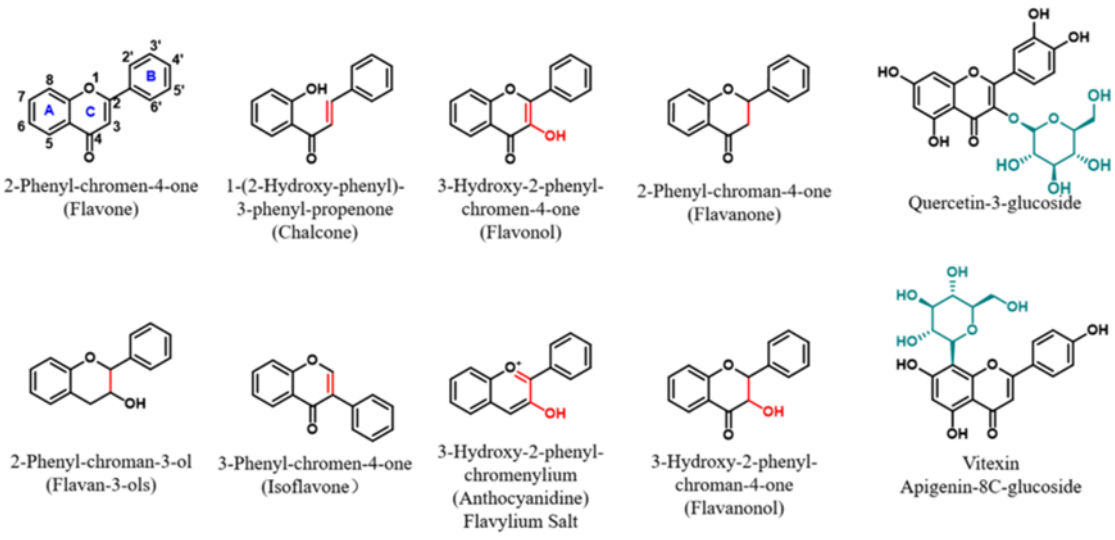


Figure 07 :Chemical-structures-of-representative-flavonoids-and-flavonoid glycosides.

(https://www.researchgate.net/figure/Chemical-structures-of-representative-flavonoids-and-flavonoid-glycosides_fig1_342022381).

6.4. Saponins

hese is a group of natural glycosides forming colloidal solutions with water which foam when shaken - thus their name. Sugars and aglycones (which are separated into steroids and terpenes according to chemical structure) are released of these glycosides by acid hydrolysis.They are devoid of nitrogen, usually odorless and with a bitter taste (excluding glycyrrhizin). Pharmacologically, saponins possess expectorant and antitussive action. When administered in small doses saponins stimulate the secretion of fluid mucus thus facilitating expectoration. **(Lacaille-Dubois, M. A & al.,2000).**

This effect is due to gastric mucus irritation which by reflex action causes an increase in bronchial secretion. After administration saponins come into contact with mucus, and their ability to reduce superficial tension makes the mucus more fluid and easy to eliminate. This irritant effect is in some cases exploited to aid the absorption of other medicines (synergic effect). If administered in higher doses saponins may induce purgative effects. In the cosmetic industry, they are used as emulsifiers in the preparation of mousses**.(Wina, E & al.,2005).**

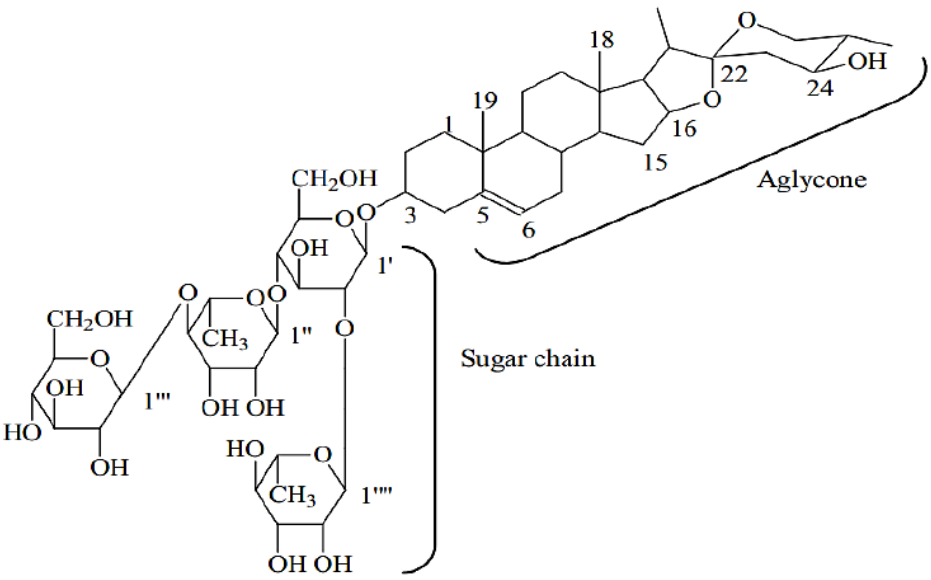


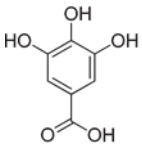
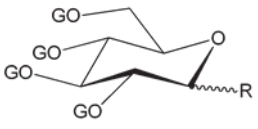
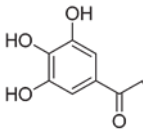
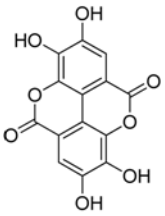
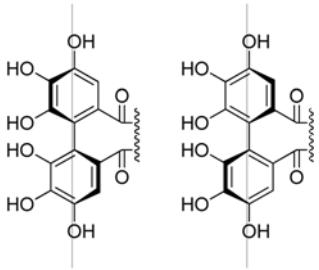
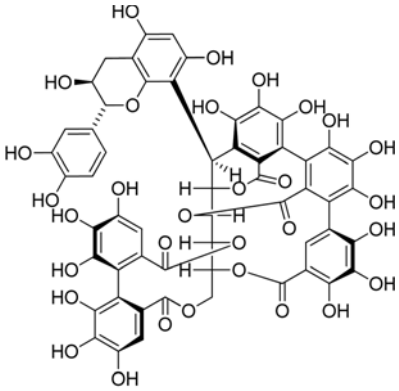
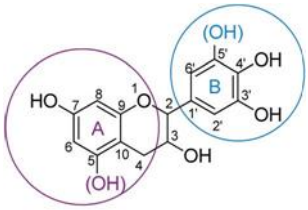
Figure 08 :Chemical-structures-of Saponins

(https://www.researchgate.net/figure/Structure-of-saponin-21_fig1_266738219)

6.5. Tannins

Tannins are polymeric phenolic compounds, water-soluble, astringent, with molecular weight ranging from 500–3000, with different biological activities. Vegetable tannins are substances well known for their many practical applications, especially in traditional medicine and the tanning industry. The tanning operation of animal skin with plant tannins has been known since antiquity and was done using the bark of different trees, especially oak species. Tannins are able to transform leather skins, precipitating proteins and forming insoluble compounds with them. Low concentrations of tannic substances, if applied locally, induce a significant reduction in vascular permeability.(**Hassanpour, S & al., 2011).**They are also employed for their astringency on rectal blood vessels, making them useful for the treatment of hemorroids. Plant drugs which are used most as sources of tannins are the leaves of Hamanelis virginiana (witch hazel), roots of Krameria triandra (rathany), rhizomes of Potentilla erecta (tormentilla), seeds of Aesculus hippocastanum (horse chestnut), leaves and husk of Juglans regia (walnut), bark of Quercus robur (oak). In plants tannins are found in complex form - tannoids - and sometimes in combination with sugars - tannosides. Tannins can be divided into two groups: hydrolysable tannins, which are split into simpler molecules on treatment with acids or enzymes, and condensed tannins (catechin tannins, also named proanthocyanidins) which give complex insoluble products on similar treatment **.(Robbins, C. T. & al.,1987) .**

Table 05 : Structure of vascular plant tannin **(Arbenz, A & al.,2015).**

Type of tannins		**Examples of structures**
Hydrolysable tannins	Gallotannins	 gallic acid  R = α,β-OH (1) TGG R = β-OG (2) β–PGG  G = Galloyl ur
	Ellagitannis	 ellagic acid  biaryl axis biaryl axis (3) HHDP
Complex tannins		 acutissimin A
Condensed tannins		 Structure of monoflavanoid

6.6. Essential or Volatile oil

Essences or essential oils consist of a complex mixture of volatile organic substances with varying chemical constitution , They are contained in particular tissues of different plants, and are usually obtained by distillation in steam currents or extraction with solvents or suitable mechanical procedures. The chemical constituents of essences are very heterogeneous: hydrocarbons, aromatics, open and closed chain terpenes, sesquiterpenes, alcohols (aromatic or terpenic), acids (aliphatic or aromatic), aldehydes and ketones (esters and ethers), phenols, various cyclic ethers, nitrogen and sulfate. **(Deans, S. G. 1991)** .Essences can be subdivided into several types. Preformed essences are the most numerous and are found in various parts of the plant.

Essential oils are present in nearly all plants, though in different quantities. The botanical families most rich in these are: Asteraceae, Lauraceae, Apiaceae, Rutaceae, Liliaceae, Magnoliaceae, Cupressaceae and Pinaceae. The pharmacological action of essence-containing drugs depends on their capacity to irritate tissue or simply by their smell and taste. Some of these essences have been found to have an important action on central nervous system or the uterine musculature.

- The pharmacological work of volatiles oils can be summed up as follows **(Francesco Capasso & al.,2003) :**

1) Antiseptic action (eucalyptus, thyme) in the lungs and kidneys.Counter-irritant action.
2) Central nervous system action (oxygenated compounds). Camphor seems to have a direct stimulatory effect on the respiratory and vasomotor centers, others act as stimulants on the motor cortex (e.g. wormwood, thuja) and can induce convulsions.
3) Antihelminthic action (wormseed).
4) Uterine stimulant action, inducing abortion in case of intoxication. Examples are rue, wormwood, savin, thuja..

Table 06 : A table showing some other active elements derived from plants and their names. **(Francesco Capasso & al.,2003).**

Class	Chemistry	Source (example)
Fatty acids	Carboxyl acide with long chain	Borage oil a lon (barago officinalis) Evening primrose(denarhera spp.) Blackcurrant oil (ribts nigrum)
glucosinolates	Glucosides containg nitrogenous and sulfur. Isothiochynate are products of glucosinolate hydrolysis	Shepherd's purse (capsella bursapastoris) White mustards (sinapis alba)
iriddios	Compounds,containing a cyclopentano-tetrahydropyranring system	Valerian (valeriana officinalis)
lectins	Protein with is not an antibody or an enzyme.But with has the ability to attach itself to specific sugars	European mistletoe(viscum album)
Lignas	Cinamyl alchol dimers	Shizandra(shizandra chinensis)
pectins	Amylas –resistant polysaccharides	Banana(musa paradisiaca)
Phyloroglucinol derivatives	Compounds containing Phloroglucin (1,3,5-Trihydroxylbenzene)	St johan's worts (hypercum perforatum)
Poly-saccharides	Macromolecule containing a larg nuber of monosaccharides (sugars formed by one unite glucose and fructose)	Echinacea (echinacea.spp) Aleo gel (aleo.spp)
purines	Methylxantine	Tea (thea senesis) Maté (ilex paragnariensis) Guarana (paullina cupana)

coumrins	Carboxylic acids with a long chain	Borage oil a lon (Barago offICinalis) Evening primrose(Denarhera spp.)

7.Overvew therapeutical from and galenical preparations

7.1. Use of medicinal plants

7.1.1. The galenical forms

For a long time, plants were used only in nature, in the form of herbal teas or powders . Now many are presented in capsules, but there are many forms of use of medicinal plants. Whatever their presentation, they enjoy a revival of interest largely aroused and maintained by advertising as well as by innumerable popularization works**. (Djordjevic, S. M. 2017)**.

More and more plants are being mixed. For these preparations, rules of good officinal practice have been introduced. Many parameters must be respected, such as the number of plants, the possible combinations, the flavour, or the taste that must be adapted to the customer. The patient's age and condition should also be taken into account. Mint, for example, will be avoided in an assertive patient .

7.1.2. Dosage forms

The galenical forms are intended to facilitate the administration of all the active principles of the medicinal plants. It is preferable to use less frequently alcoholic preparations and uncomplicated classical extracts whose active ingredients are sometimes altered. Now many more practical forms exist. For example, dry powdery extracts. **(Kumadoh, D. O. R. I & al.,2017)**. They are obtained by the desiccation of extractive solutions using processes such as lyophilization or nebulization. Alone or in combination, these dry extracts are presented in powdered tablets, and especially in capsules sometimes confused with powdered plant capsules on which they have the advantage of a greater concentration of active ingredients.

Among the various existing forms, the active ingredient may have different aspects. It is initially in the form of powder, extract or tincture and is called a Galenic form .

- **The raw material comes in three potential forms:**

1. **Fresh plants:** They serve as the basis for the preparation of mother tinctures, which in turn allow the development of homeopathic medicines .
2. **Dry plants :** They are the basis of dyes, nebulizates, extracts, but also powders.
3. **Stabilized plants :** The enzymatic potential of the plant is annihilated by the action of alcohol or heat, allowing the preservation of the constituents in their original state. These plants make it possible to obtain intraits . Horse chestnut (Aesculus hippocastanum L.) can be used in this form during a hemorrhoidal attack.

7.2. The effect of principe active drug ingredients on the human body

The entire course of action of a drug, from dose to effect, can be understood in three phases:

1. Drug administration phase.
2. Pharmacokinetic phase.
3. And pharmacodynamic phase

This useful conceptual framework, based on the principles offered by Ariëns and Simonis, organizes the steps of a drug's action from drug administration (method by which a drug dose is made available to the body) through effect and ultimate elimination from the body. The drug administration phase entails the interrelated concepts of drug formulation (e.g., compounding a tablet for particular dissolution properties) and drug delivery (e.g., designing an inhaler to deliver a unit dose). **(Wang, X & al., 2013).**Two key topics of this phase are the drug dosage form and the route of administration. The drug dosage form is the physical state of the drug in association with nondrug components. Tablets, capsules, and injectable solutions are common drug dosage forms. The route of administration is the portal of entry for the drug into the body, such as oral (enteral), injection, or inhalation. The form in which a drug is available must be compatible with the route of administration desired. The injectable

route (e.g., intravenous route) requires a liquid solution of a drug, whereas the oral route can accommodate capsules, tablets, or liquid solutions.

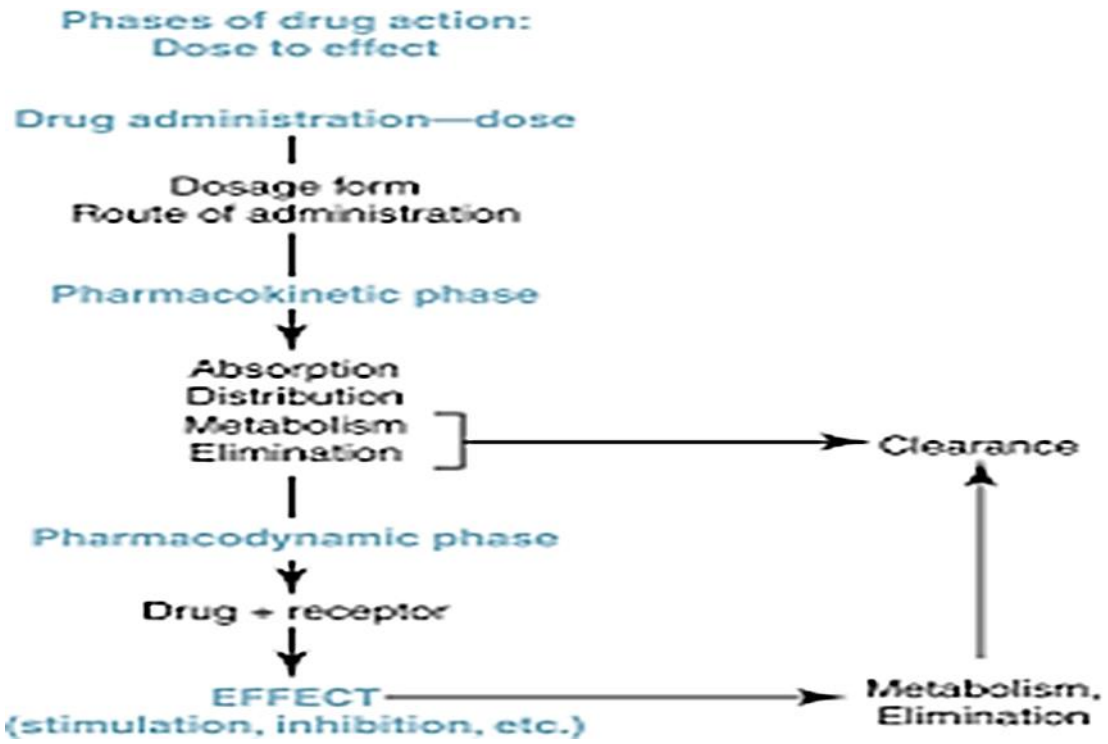


Figure 09: Conceptual scheme illustrating the major phases of drug action in sequence, from dose administration to effect in the body**. (Katzung BG, 2009).**

7.3. Medicinal extracts rules and uses (risks and adverse reactions)

Herbal medicine was usually practiced following a medical prescription or on the advice of a doctor. From then on the patient came to the dispensary with his prescription or already knowing what he wanted.However, self-medication is being practised more and more. It is being done without a diagnosis, without a doctor. It is purely symptomatic, according to the indications of the boxes or associated leaflets, the knowledge acquired in the basic works and the articles of the general public press.

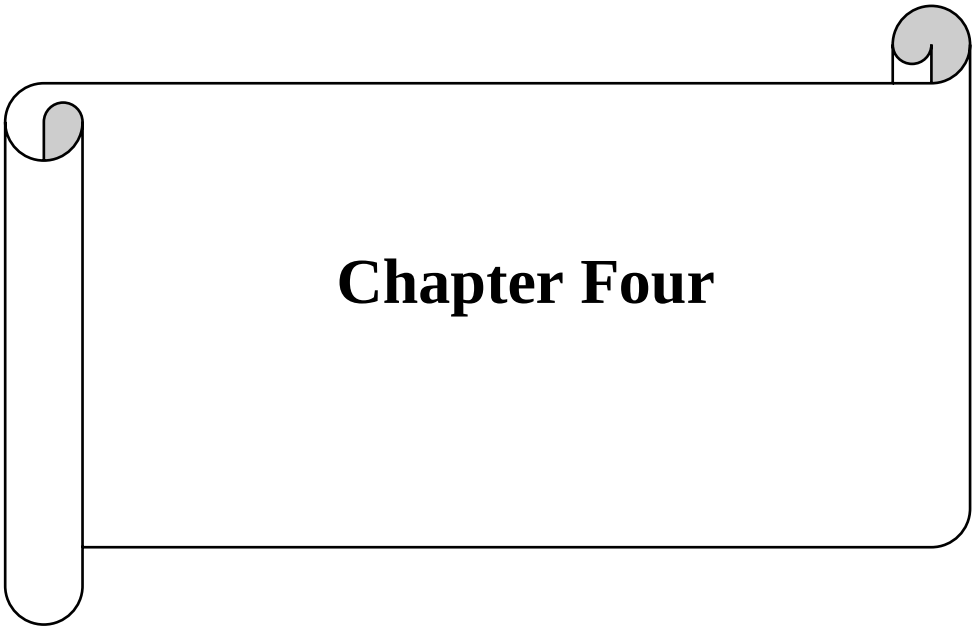
The first risk is plant toxicity. Although selected by the Agency's Cahiers for their safety, medicinal plants can, like any drug, be toxic if they are ingested in too large quantities. In this

case, as soon as a plant is found to be toxic, it is removed from this well-established list of traditional medicinal plants. **(Francesco Capasso & al.,2003).**

1. Another possible adverse effect is intoxication . This kind of problem after taking plants is always possible, even after controlling the plants. Indeed a product can be misused by the patient, over too long a period or with a wrong indication. The common example is the thinning diet by plants. The patient who is being treated voluntarily increases her dosages thinking that she will obtain an increase in the effectiveness of the treatment.
2. Another risk that should not be excluded is the falsification of medicinal plants. Voluntary or involuntary, it can have serious consequences for the user. One of the main causes of falsification of medicinal plants is their cost. This is the case of saffron (Crocus sativus L.) from which a spice is extracted. This one, expensive, is often replaced by another similar; and this since the dawn of time.

Finally, we could not close this chapter without talking about a recurring problem in Herbal Medicine: adulteration of products. This term is used to indicate the intentional addition of undeclared substances to an herbal product. It takes different forms. The former results in the addition of compounds for the drugs in question in order to increase the final weight of the product by incorporating material such as a cheap plant, or sometimes even lead.

Some forms of adulteration pose real health risks. This is the case when adding undeclared medicines with herbal products. Amphetamines, narcotics, barbiturates, corticosteroids and other antibiotics are commonly found in plants from some countries . Studies have shown that the rates of pharmaceutical adulteration of patented Asian medicinal plants range from 7 to 23.7percent.



Chapter Four

1. Mode of action hallocinogens moluculars

1. Natural products of hallucinogens plants

Hallucinogens, including those derived from plants, are a special case when discussed in relation to the development of therapeutic drugs. The idea that hallucinations may be a reasonable therapeutic option in certain situations is not an acceptable doctrine for Western medicine, despite the abundance of anecdotal evidence from shamanic traditions suggesting that hallucinogens can often be effective at alleviating causes (or at least symptoms) of many diseases such as psychiatric disorders, if not physical ones. **(McKenna, D. J. 1995)**.

While the potential therapeutic value of the drug trial briefly attracted the attention of the psychiatric community several decades ago, efforts to develop "scientific" validation of hallucinations have been largely abandoned. Some argued that this abandonment had occurred largely in response to political and societal pressure, not because the psychedelic model of treatment had been investigated and found acceptable. **(Shulgin, A.T& al.,1991).**

In these following tables : active varieties of seed plants (126 genders) previously used by humans have been assembled to date.

Table N°07 : Active varieties of seed plants previously used by humans have been assembled to date **.(Alrashedy, N. A & al.,2016).**

Acanthaceae (Lamiales)	*Justicia pectoralis* Jacq.	Justicia	Native American (*Rätsch,2005*
Acoraceae (Acorales)	*Acorus calamus* L.	sweet flag	Indomalayan, Temperate Asian (*Rätsch, 2005*)
Aizoaceae (Caryophyl-lales)	*Sceletium* spp.	kougoed	African and Middle Eastern (*Gericke & Viljoen, 2008*)
Apiaceae (Apiales)	*Angelica sinensis* (Oliv.) Diels	dong quai	Temperate Asian (*Rätsch,2005*)
Apiaceae (Apiales)	*Centella asiatica* (L) Urb.	gotu kola	Indomalayan, Temperate Asian (*Rätsch, 2005*)
Apocynaceae (Gentianales)	*Alstonia scholaris* (L.) R. Br.	dita	African and Middle Eastern, Australasian, Indomalayan (*Rätsch, 2005*; *Arulmozhi et al.,2012*)

Apocynaceae (Gentianales)	*Apocynum venetum* L	luobuma	Temperate Asian (*Grundmann et al., 2007*)
Apocynaceae (Gentianales)	*Carissa edulis* (Forssk.) Vahl	Arabian numnum	African and Middle Eastern (*Rätsch, 2005*)
Apocynaceae (Gentianales)	*Rauvolfia serpentin* (L.) Benth. ex Kurz	snakeroot	Indomalayan (*Mamedov, 2005*)
Apocynaceae (Gentianales)	*Tabernaemontana* spp.	milkweed	Indomalayan, African, Native American (*Rätsch, 2005*)
Apocynaceae (Gentianales)	*Tabernanthe iboga* Baill.	iboga	African and Middle Eastern (*Sayin, 2014*)

Apocynaceae (Gentianales)	*Voacanga* spp.	voacango bush	African and Middle Eastern (*Rätsch, 2005*)
Aquifoliaceae (Aquifoliales)	*Ilex* spp.	yerba mate	Native American (*Rätsch, 2005*)
Araliaceae (Apiales)	*Panax ginseng* C.A.Mey.	ginseng	Temperate Asian (*Rätsch, 2005*)
Arecaceae (Arecales)	*Areca catechu* L.	betel nut	Indomalayan (*Rätsch, 2005*)
Asteraceae (Asterales)	*Artemisia* spp.	wormwood	European; Temperate Asian (*Rätsch, 2005*; *Sayin, 2014*)
Asteraceae (Asterales)	*Calea ternifolia* Oliv	dream herb	Native American (Rätsch, 2005)
Asteraceae (Asterales)	*Lactuca virosa* Habl.	wild lettuce	African and Middle Eastern (*Rätsch, 2005*)
Asteraceae (Asterales)	*Tagetes* spp.	Mexican marigold	Native American (*Rätsch, 2005*)
Bignoniaceae (Lamiales)	*Bignonia nocturna* (Barb.Rodr.) L.G.Lohmann [=*Tanaecium nocturnum* (Barb.Rodr.) Burea & K.Schum.]	koribo	Native American (*Rätsch, 2005*)
Burseraceae (Sapindales)	*Boswellia sacra* Flueck.	olibanum tree	African and Middle Eastern (*Rätsch, 2005*)

Cactaceae (Caryophyl-lales)	*Ariocarpus fissuratus* (Engelm.) K.Schum.	chautle	Native American (*Rätsch, 2005*)
Cactaceae (Caryophyl-lales)	*Echinopsis* spp. (incl. *Trichocere us pachanoi* Britton & Rose)	San Pedro cactus	Native American (*Rätsch, 2005*)

2.Evolution of the course of plant hallucinations and therapeutic drugs in medical trials

No drug group has experienced more controversy and confusion in this century than the category of drugs referred to as "hallucinogens" or "narcotics**".(Grob, C. S & al.,1998)**. Each of these terms involves a different direction of the effects, actions and the importance of these drugs by those who used them and wrote about them. Different factions called them what they perceive to be their specific attributes and medical literature often refers to them as hallucinogenic, ordinary journalism as psychedelic (a term coined by Humphrey Osmond referring to "showing reason").

Lack of objective information about hallucinations and their use deprived them of knowledge of how to structure safe use and reduce risks. Enthusiasm for hallucinations to induce positive situations of change has been replaced by fear that they are instead serious risks to public health. As that have been excluded from psychological and medical discourse, while increasing attention has been paid to the risks of unsupervised use**.(Lynch, W. J & al.,2002).**

3. The botanical and chemical distribution of hallucinogens

Among the wide range of species in the miscellaneous plant esti that mated from 200,000 species and were employed in primitive societies for thousands of years to stimulate visual, auditory, tactile and other hallucinations. Due to their often descriptive non-terrestrial effects, they were usually considered sacred and played central roles as sacred markers in indigenous religions **(Schultes, R. E. 1969).**While psychoactive species are widely scattered throughout the plant world, they appear to be concentrated more or less amongst the fungi and the angiosperms. The bacteria, algae, lichens, bryophytes, ferns, and gymnosperms seem to be notably poor or lacking in species with hallucino genic properties **(Schultes, R. E. 1970).**

Scientific interest in hallucinogenic agents has recently been intense, partIy because of the hope of finding potentially valuable drugs for use in experimental or even therapeutic psychiatry and also for use as possible tools in an explanation of the biochemical origins of mental abnormalities**.(Jarvik, M. E. 1968) .** Hallucinogens are most likely to result in adverse reactions that necessitate the intervention of health professionals and law enforcement when they are taken in uncontrolled environments. However, research suggests the

therapeutic potential of hallucinogens when administered under clinical protocols that preserve hospitals' ethical and clinical responsibilities. Further basic and translational research on the efficacy of hallucinogens in the treatment of alcoholism, OCD, and cluster headache is warranted, as is their use as a tool for probing the molecular and neuronal circuit mechanisms of psychotic states.

4. Origine of hallucinogens

Psychoactive plants contain chemicals that are supposed to have evolved as alchemical chemicals, but target specific neural receptors when consumed by humans, changing cognition, emotion and cognition. These plants have been used since ancient times as medicines and in the context of religious rituals for their various psychological effects (such as hallucinogens, stimulants, sedatives). The prevalence of psychoactive plants in different cultures stimulates the investigation of the commonalities of these plants, where the framework of racial genetics may be insightful. Addiction arises from wanting to re-experience the pleasure due to the drug's ability to cause dopamine buildup **(Lüscher & al., 2006).** Compounds that mimic serotonin and act as receptor agonists like mescaline in the peyote cactus (Lophophora williamsii, Cactaceae), trigger hallucinations and cognitive breakdown **(Polya, 2003)**. Stimulating substances, such as the alkaloid nicotine in tobacco, Nicotiana tabacum (Solanaceae), mimic the endogenous neurotransmitter acetylcholine stimulating muscle contractions and cholinergic areas of the brain involved in arousal and attention (Polya, 2003). Yet, the confamilial Atropa belladonna, contains a chemically different alkaloid, atropine, which promotes sedation and incapacitation via its action as muscarinic acetylcholine antagonist, blocking neuromuscular communication (**Spinella 2001).**

Hallucinogenic molecules are divided into two broad groups: nitrogen and non-nitrogen Vehicles. (**Berridge, M & al.,1973).**

The nitrogenous compounds : play by far the greater role and comprise, for the most part, alkaloids or related substances, the majority of which are, or may be biogenetically derived from, the indolic amino acid tryptophan. They may be classified into the following groups :

1. β -carbonile
2. Ergolines
3. Indoles

4. Isoquinolines
5. Isoxazoles
6. β -phenylethylamines
7. quino lizidines
8. tropanes
9. tryptamines

Non-nitrogenous compounds : which are the active principles in at least two well-known hallucinogens include .

- ❖ dibenzopyrans
- ❖ phenylpropenes

other compounds, such as cate-chols and alcohols, may occasionally play a role.

4.1. Nitrogenous principles

4.1.1. β –CARBONILE

1.Zygophyllaceae : "Peganum.the syrian rue or Peganum Harmala"; is an herb found in dry localities from the Mediterranean area east to India, Mongolia, and Man churia. It is a member of a genus of six species distributed in dry areas of Asia Minor and Asia and in southwestern United States and Mexico. AI· though this and other species of have l ong been esteemed in folk medicine, its purposeful employment as an hallucinogen is open to question, vague reports notwithstanding, even though it does have psychotomimetic principles **(Porter, D. M. 1972).** The seeds of Peganum Harmala contains harmine, harmaline, harmalol, and harman, bases of a typical (J-carboline structure of wide botanical and geographical distribution, having been isolated from at least eight plant families of both the New and the Old World . **(Deulofeu, V. 1967).**

Figure 10: Illustration of Zygophyllaceae**("Zygophyllaceae R. Br., nom. cons". Germplasm Resources Information Network. United States Department of Agriculture. 2003-01-17. Retrieved 2009-09-25.)**

2.Malpighiaceae : Banisteriopsis.- In the wet tropical forest areas of northern South America, indigenous people use them as hallucinogens. Several types of Banisteriopsis contain ¬ alkalis: B. Caapi, B. Inebrians. **(Friedberg, C. 1971).**

A genus of some 100 species of tropical America, Banisteriopsis is tax¬ onomically still rather poorly understood. This is true especially of B. Caapi and B. Inebrians, partly because of the lack of fertile material for study of these infrequently flowering j ungle lianas, even though the first botanical attention to this drug plant dates from 1854, when it was first encountered in northwestern Brazil by the explorer Spruce**. (Schultes, R. E. 1963).**

More recent examination of plant-documented substances of this type has established the presence of these substances in bark and sometimes in damage leaves as well as in fewer occasional amounts of harmaline and THC Deulofeu,V.,in Ethnopharmacologic Search for Psychoaciface. Recent investigations on B. Inebrians have isolated damage from stems and precise amounts of what appears to be harmful. An interesting chemical study of B. Caapi group-type stems, although some 115 years have passed, has indicated a harmful presence in concentrations identical to those found in newly collected substances. **(Schultes, R. E. 1963).**

Figure 11: Illustration of Malpighiaceae **("Malpighiaceae Juss". tropicos. missouri botanical garden. archived from the original on 2011-07-22. retrieved 2010-02-02.).**

4.1.2.Ergolines

1.Convolvulaceae :Ipomoea, Rivea.-The early Spanish chroniclers of Mexico reported that the Indians employed in their religious and magic rites an hallucinogenic seed cal1ed ololiuqui by the Aztecs. It was also used medicinally, and when ap plied as a poultice was said to have analgesic properties.Known as coatl-xoxouhiqui ("snake plant") , it was adequately illustrated as a morning glory. Although several Mexican botanists accepted this identi fication during the last century, not until 30 years ago was a voucher specimen of a convolvulaceous plant, the seeds of which were employed as a divinatory hallucinogen, collected amongst the Mazatecs of Oaxaca and determined as Rivea corymbosa. Later field work uncovered similar uses of another morning glory, Ipomoea violacea, amongst the Zapotecs, also of Oaxaca; this species represents possibly the narcotic tlitliltzin of the ancient Aztecs **(Schultes, R. E. 1970).**The main psychotomimetic constituent of the seeds of both species are ergine (d-Iysergic acid diethylamide) and isoergine (d-isolysergic acid diethyl amide) which occur together with minor alkaloids: chanoclavine, elymo cIavine, and Iysergol. Ergometrine appears to be present in seeds of I. violacea but absent in R. corymbosa. The total alkaloid content of R. corymbosa seed is 0.012%; of I. violacea, 0.06%-and, indeed, Indians use smaller quantities of the latter than of the former **(Hofmann, A. 1961).**

The discovery of ergot alkaloids-constituents of Claviceps purpurea, a relatively primitive fungus-in one of the phylogenetically most advanced angiosperm families was unexpected and is of great chemotaxonomic interest. Suspicion that fungal spores might have contaminated the convolvulaceous seeds was ruled out experimentally ; and the discovery of these alka loids in fresh leaves, stalks, and roots of I. violacea and, to a minor extent, in leaves

of R. corymbosa indicated that these constituents are produced by the tissue of the morning glories themselves, not by infecting fungi. (**Berridge, M & al.,1973).**Large amounts of a new glycoside, turbicoryn, were likewise isolated from seeds of R. corymbosa, but this compound apparently has no part in the psychotomimetic action .Studies have shown the presence of these ergot alkaloids in a number of horticultural "varieties" of I. violacea and other species of Ipomoea, as well as in the related genera A rgyreia and Stictocardia**.**

Figure 12 : Illustration of Convolvulaceae **(Ulrike Steiner & al.,2006).**

4.1.3.Iboga-Indole

1.Apocynaceae :Tabernanthe.-Probably the only member of this alkaloid-rich family known definitely to be utilized as an hallucinogen is iboga, the yellowish root of Tabernanthe Iboga. This narcotic is of great social importance, especially in Gabon and nearby portions of the Congo in Africa. The use of iboga, first reported by French and Belgian explorers in the middle of the last century, appears to be spreading. In Gabon, it is employed in initiation rites of secret societies, the most famous of which is the Bwiti cult. Sorcerers take the drug before communicating with the spirit world or seeking advice from ancestors **(Berridge, M. J& al.,1973).**

Figure 13 : Illustration of Apocynaceae **(retrieved from angiosperm phylogeny website, version 13)**

Twelve closely related indole alkaloids have been reported from ibogaj they comprise up to 6% of the material. Ibogaine, apparently the principal psychoactive alkaloid, acts as a cholinesterase inhibitor, a strong central stimulant, and as an hallucinogen.**(Jarvik, M. E.1968).** Tabernanthe is a genus of about seven species native to tropical Africa.Sometimes other plants-occasionally as many taken with iboga, but few have been chemically investigated. One of the most interest ing, the euphorbiaceous A lchornea floribunda, is employed also in the same way as iboga in another secret society in Gabon but is apparently not hallucinogenic. Its active principle seems to be the indole yohimbine**(Tyler, V. E & al.,1966) .**

4.1.4. Isoquinolines

1.Cactaceae : Lophophora.-Lophophora Williamsii, the peyote cactus, has more than 30 bases belonging to the phenylethylamines and the simple isoquinolines. **(Agurell, S. 1969)**,. The visual hallucinations are due to the phenylethylamine mescaline , but other aspects of the complex peyote-intoxi cation, such as auditory, tactile, and taste hallucinations and other effects, may be due in part at least to the isoquinolines, either alone or in combina tion. Among the important isoquinolines present are anhalamine, anhalidine, anhalinine, anhalonidine, pellotine, lophophorine, peyoglutam, mescalotam, and several as yet unnamed bases recently isolated .

Figure 14 : Illustration of Various_Cactaceae **(Angiosperm Phylogeny Group 2009).**

4.1.5.Isoxazoles

1.Agaticaceae : The genus A manita, of from 50 to 60 species, is cosmopolitan, occurring on all continents except South America and Australia, but the species occupy definitive areas. A number of the species are toxic, and their chemical con¬ stitution, still poorly understood, appears to be variable. Amanita.-While Amanita muscaria-thefly agaric, a mushroom of the north-temperate zone of Eurasia and North America-may represent one of the oldest of the hallucinogens used by man, only very recently has a clarifi¬ cation of the chemistry of its active principles begun to take shape **.(Wasson, R. G. 1963)** .In the 18th Century, Europeans discovered the narcotic use of Amanita muscaria among primitive tribesmen of Siberia.

Recent chemical and pharmacological studies have shown that the principal biologically active constituents appear to be muscimole, the enolbetaine of S-aminoethyl-3-

hydroxy-isoxazole--an unsaturated cyclic hydroxamic acid which is excreted in the urine; and ibotenic acid, the zwit¬ terion of a-amino-a-[3-hydroxy-isoxazoylyl-(5)]-acetic acid monohydrate. The less active musoazone, likewise an amino acid, a-amino-a[2(3H)-oxazolonyl-(5)]-acetic acid, is present in varying but lesser amounts. Structurally related to these isoxazoles is the antibiotic oxamycine which often has psychoactive effects-mental confusion, psychotic depression, abnormal behavior-in man. Other active substances structurally still not elucidated are also known to be present **.(Jarvik, M. E.1968).**

Figure 15: Illustration of Agaticaceae **(Poinar G, Singer R 1990).**

4.1.6. Phenylethylamines

1.Cactaceae : Lophophora.-One of the Ancicenatctsaacceraeed hallucinogens of Mexico, still in use, is the small, grey-green, napiform, spineless cactus peyote: Lophophora Williamsii. It might well be called the "prototype" of hallucinogens since it has been one of the most spectacular psychotomimetics known. It was first fully described by the early Spanish medical doctor Francisco Hernandez, but many other colonial Spanish chroniclers detailed the strange story of peyote. Peyote rites persist in several tribes of northern Mexico. It was used in Texas in 1760, was known among American Indians during the Civil War, but came to public attention in the United States about 1880, when the Kiowas and Comanches elaborated a typical Plains Indian vision-quest ritual around its ceremonial ingestion. The peyote cult, organized as the Native American Church, has gradually spread to many tribes in the United States and Canada and counts 250,000 adherents **(Albaugh, B. J & al.,1974)**, **(Schultes, R. E & al.,1969-1970)**. The chlorophyll-bearing crown of the cactus, dried

into discoidal "mescal buttons" which are virtually indestructible and can be shipped long distances, is eaten .

Figure 16: Illustration of Lophophora **(C. A. Butterworth & al., 2002).**

4.1.7.Quinolizldlnes

1.Leguminosae : Cytisus (Genista).-The hallucinogenic use by Yaqui medicine men in northern Mexico of Cytisus (Genista) canariensis, a shrub native to the Canary Island, not Mexico, has recently been reported **(Fadiman, J. 1965)** . It is rich in the toxic alkaloid cystisine (ulexine, baptitoxine, sophorine) which occurs commonly in the Leguminosae . About 25 species of native to the Atlantic Islands, Europe, and the Mediterranean area, are known, and a number of the species are toxic.

Sophora.-A shrub of dry areas of the American Southwest and adjacent Mexico, Sophora secundiflora yields the socalled mescal beans or red beans. Mexican and Texan Indians formerly employed these beans in the ceremonial Red Bean Dance as an oracular and divinatory medium and for visions in initiation rites. **(Schultes, R. E .1969-1970).** Its use died out in the United States with the arrival of peyote, a much safer hallucinogen. Mescal beans, which contain cytisine, are capable of causing death by asphyxiation . Historical reports of the mescal bean go back to 1539, but archaeological remains suggest their ritualistic use earlier than 1000 A.D.. Sophora, with some 50 species, occurs in tropical and warm temperate parts of both hemispheres.

Figure 17 : Illustration of Cytisus (Genista).**(Sunset editors 1995).**

2.Lythraceae : Heimia.-Heimia salicifolia has been valued in Mexican folk medicine since earliest times. Known as sinicuichi, its leaves are wilted, crushed in water, and the juice set in the sun to ferment. The resulting drink is mildly intoxicating. Alkaloids were first reported from H. salicifolia in 1958 **(Hegnauer, R & al.,1958) .** Recent work has isolated and characterized five alkaloids, of which the major psychoactive one appears to be cryogenine (vertine) **(Blomster, R. N & al.,1964) ,** Differing from the usual quinolizidines in having the quinolizidine as part of a larger and complex system of rings, cryogenine has been found only in the Lythraceae. The genus Heimia comprises three hardly distinguishable species and ranges from southern United States to Argentina .

Figure 18: Illustration of Heimia_salicifolia_flowers **(germplasm resources information network (grin). agricultural research service (ars), united states department of agriculture (usda). retrieved 2010-03-20).**

4.1.8.Tropanes

1.Solanaceae :A tropa.-The belladonna plant, A tropa Belladonna, was utilized as an hallucinogen in Europe in medieval witches' brews. Its principal active constituent has long been known to be scopolamine, but minor tropane alkaloids are also present **.** There are four species of Atropa, distributed in Europe, the Mediterranean area, and from Central Asia to the Himalayas Datura, Methysticodendron.-Datura hasa long history as an hallucinogenic genus in both hemispheres . The genus, comprising some 15 to 20 species, is usually divided into four sections: (a) Stramonium, with three species in the two hemispheres: (b) Dutra, comprising six species) ;c) Ceratocaulis, with one Mexican species; (d) Brugmansia, South American trees representing possibly six or seven species. **(Avery, A. G & al.,1959).**

Figure 19 : Illustration of Atropa Belladonna.**(Kennedy, David O. 2014).**

4.1.9.Tryptamines

1. Acanthaceae lusticia. The Waikas of the Orinoco headwaters in Venezuela and in northern Amazonian Brazil occasionally dry and pulverize the leaves of lusticia pectoralis var. stenophylla as an admixture to their Virola-snuff . There are suspicions that this aromatic herb may contain tryptamines (Holmstedt, personal communication). If the preliminary indi cations can be verified, it will for the first time establish the presence of these indoles in the Acanthaceae. There are more than 300 species of lusticia in the tropical and subtropical parts of both hemispheres.

2. Agaricaceae : Conocybe, Panaeolus, Psilocybe, Stropharia.-The Spanish conquerors found Mexican Indians practicing religious rites in which mushrooms were ingested as a sacrament permitting them to commune through hallucinations with the spirit world. The Aztecs knew these "sacred" mushrooms as teonanacatl ("food of the gods") **(Jarvik, M. E. (1968) , (Schultes, R. E. (1970).**

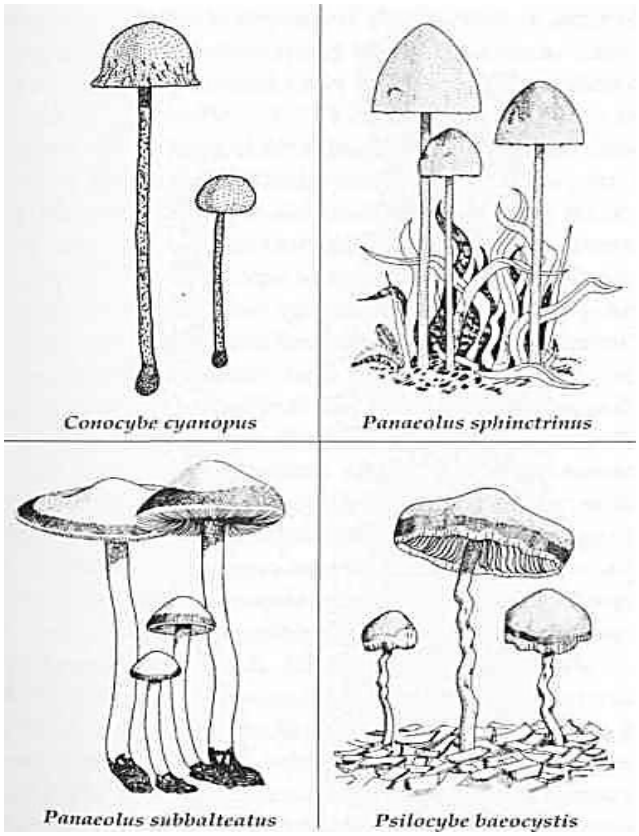


Figure 20: Illustration of Conocybe, Panaeolus, Psilocybe, Stropharia **.**

(Poinar G& al.,1990).

3.Leguminosae : Anadenanthera.-The New World snuff prepared from beans of A naden anthem (Piptadenia) peregrina, known in the Orinoco basin of Colombia and Venezuela, center of its present use, as yopo or nopo, represents probably the cohoba encountered in Hispaniola by Columbus' second voyage in 1496. Von Humboldt, Spruce, and other explorers who mentioned it were all astonished at its hallucinogenic potency Five indoles have been isolated from A. peregrina, chief of which are N- dimethyltryptamine and bufotenine (5-hydroxy-N, N-dimethyltrypt amine . The beans contain as their main constituent N, N-dimethyl tryptamine or bufotenine. Other indoles found in this species are 5-methoxy N,N-dimethyltryptamine, N-monomethyltryptamine and 5-methoxy-N monomethyltryptamine.

4.Malpighiaceae : Banisteriopsis.-One of the numerous admixtures of the ayahuasca caapi-yaje drink prepared basically from bark of Banisteriopsis Caapi or B. inebrians (which contain ,B-carboline bases) is the leaf of B. Rusbyana, known in the western Amazon of Colombia and Ecuador as oco-yaje. The natives add the leaf to heighten and lengthen the visions. Recent examina tion indicates that B. Rusbyana has in its leaves and stems, to the exclusion of the harmala alkaloids characteristic of the other two narcotically utilized species, N,N-dimethyltryptamine and traces of other tryptamines (Na- methyltryptamine; 5-methoxy-N-dimethyltryptamine; B-methyltetrahydro-,B-carboline) **(Schultes, R. E. 1970).** Tryptamines have apparently not hitherto been reported from the Malpighiaceae.

Figure 21: Illustration of Banisteriopsis**.(de Frias, U. A & al.,2012).**

3.Myristicaceae : Virola.-Hallucinogenic snuffs are prepared in northwestern Brazil and adjacent Colombia and Venezuela from the reddish bark resin of Virola, a genus of 60 to 70 trees of Central and South America. The species employed have only recently been identified as V. calophylla and V. calophylloidea in Colombia and V. theiodora in Brazil.**(Jarvik, M. E.1968)**.The most intense use of this snuff, called yakee, paricd, epend, and nyakwana, centers among the Waikas of Brazil and Venezuela. In Colombia, only witch doctors employ it, but in Brazil the intoxicant is taken by all adult males, either individually at any time or ritually in excess at endocannibalistic ceremonies amongst the Waikas. The resin, which is boiled, dried, pulverized, and occasionally mixed with powdered leaves of a Justicia and bark-ashes of Theobroma subincanum or Elizabetha princeps, acts rapidly and violently. Effects include excitement, numbness of the limbs, twitching of facial muscles, nausea, hallucinations, and finally a deep sleep; macroscopia is frequent and enters into Waika bliefs about the spirits resident in the drug.

Figure 22 : Illustration of Myristicaceae **. (Bingtao Li & al.,2008)**

Figure 23: Illustration of Virola.**(Torres, C. M & al.,1991).**

4.Rubiaceae : Psychotria.-Among the sundry admixtures employed to "strengthen" and "lengthen" the effects of the hallucinogenic drink prepared from Banisteriopsis Caapi and B. inebrians in the western Amazon, one of the most commonly added are leaves of Psychotria . One species used in Ecuador and Peru, P. viridis [reported through a misidentification as P. psychotriaefolia , has recently been shown to contain N,N-dimethyltryptamine (Der Marderosian, personal communication). The same species and another not yet specifically identified are similarly used in Acre Territory, Brazil **(Prance, G. T. 1972).** Tryptamines have apparently not hitherto been reported from the Rubiaceae. The genus Psychotria comprises more than 700 species of the warmer parts of both hemispheres, many of which have im portant roles in folk medicine or are poisons .

Figure23 : Illustration of Psychotria.

("Psychotria in the World Checklist of Rubiaceae". Retrieved 5 April 2016)

5 .Non-Nitrogenous Principles

5.1.Dibenzopyrans

1.Cannabaceae : Cannabis.-The most impoCrtaannntaboaf ctehaee non-nitrogenous hallucinogens are the dibenzopyrans found in Cannabis sativa, source of marij uana, hashish, bhang, ganja, and other narcotic products. Cannabis, a monotypic genus sometimes placed in the Moraceae but often allocated, together with the hops plant (Humulus), in a separate family, Cannabaceae, represents perhaps one of the oldest and certainly the world's most widespread hal lucinogen. The source also of hempen fibres and of an edible seed-oil, the plant is native probably to central Asia but is now found cultivated or spontaneous in most parts of the world. It is represented by many agricul tural varieties and ecological races or strains, some of which are rich, some poor, some even lacking in the intoxicating principles.

The biodynamic activity of Cannabis is due to a number of constituents contained in a red oil distilled from the resin, mainly to a mixture of stereo isomers collectively called tetrahydrocannabinols and sundry related com pounds, including cannabinol, cannabidiol, cannabidiolic acid, cannabigerol, and tetrahydrocannabinolcarboxylic acid**, (Schultes, R. E. 1970)**. The compound l-tetrahydrocannabinol has recently been shown to be the principal biologically active constituent of *Cannabis* . Cannabichrome has like wise been reported as active. Cannabinol and cannabidiol are devoid of euphoric properties, although cannabidiol, when heated with an acidic catalyst, may be converted into an active mixture of tetrahydrocannabinols, a conversion that may be effected during the smoking of *Cannabis.*

Cannabi gerol and cannabidiolic acid are sedative, and the latter compound has antimicrobial properties . Cannabinol and the tetrahydrocanna binols have been synthesized. The first biologically active principle to have been structurally elucidated and synthesized was 1-2,3-trans tetrahydro cannabinol .

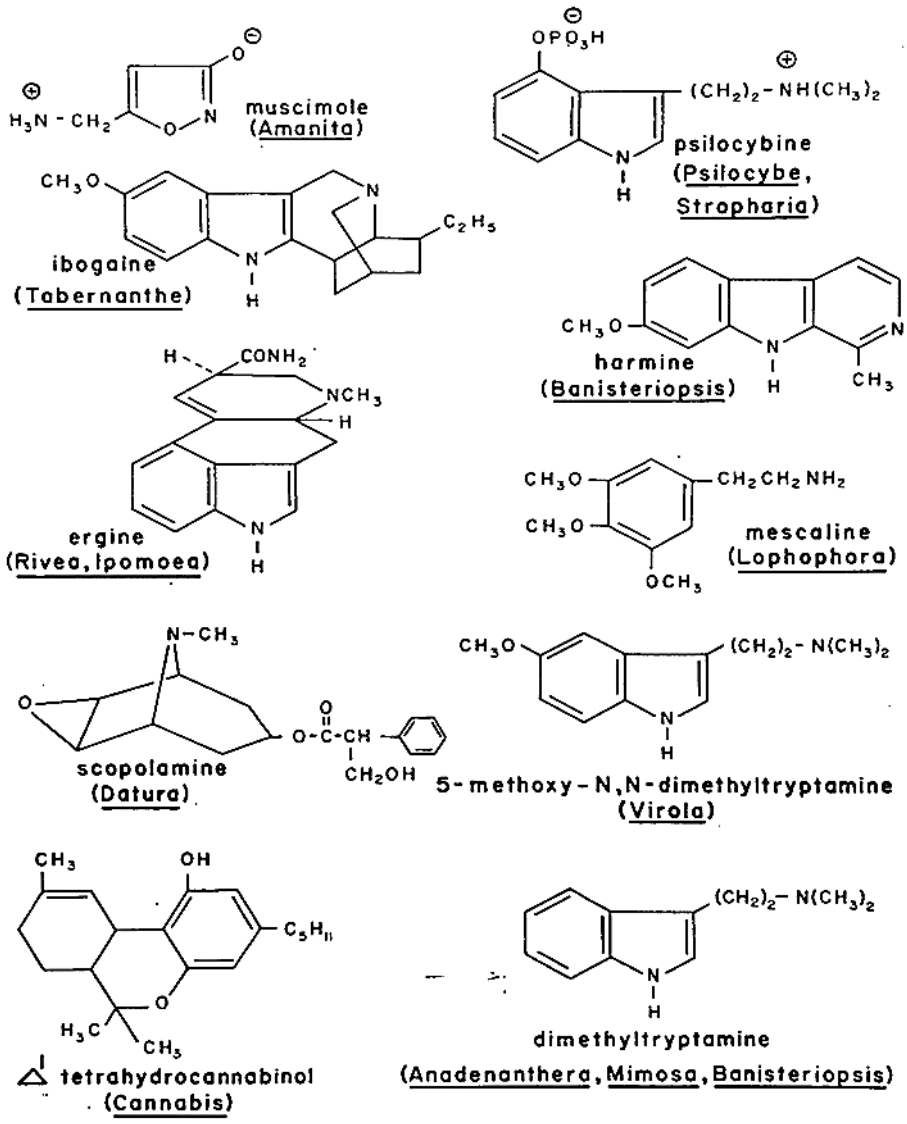


Figure 25 : Image highlighting the main bioactive ingredients of cannabis.

(Berridge, M. J & al., 1973).

When heated with an acid stimulus, it can be converted into an active combination of THC, a conversion that can occur while smoking cannabis. Cannabis-gerol and hemp acid is soothing, and the latter compound has antimicrobial properties. Cannabinol and tetrahydrocana were manufactured . The first bioactive principle structurally articulated and synthesized was 1-2, 3-trans tetrahydro cannabinol**. (Solowij, N. 1998).**

5.2.Phenylpropenes

1.Myristicaceae : Myristica.*The* tree that yields the spices nutmeg and Mace-Myristica *fragrans-is* thought to have been employed aboriginally as a narcotic in southeastern Asia, where it is native. It is sometimes used as an hallucino gen in sophisticated circles in Europe and North America and has occasion ally become a problem in prisons in the United States **(Jaiswal, P & al.,2009).**

Although its toxicology has not yet been wholly elucidated, the psychoactive principles are contained probably in the essential oil of the seed and aril. The composition of nutmeg oil is highly variable, both qualitatively and quantitatively, but it does contain fatty acids, terpenes, and aromatics. The psychopharmacological effects may be attributable to several phenyl propenes. Elemicine, myristicine, and safrol have been suggested as the active constituents of the oil, which may also contain eugenol, isoeugenol, methylisoeugenol, methoxyeugenol, methyleugenol, and isoelemicine. It seems doubtful that myristicine or safrol are responsible for a significant part of the hallucinogenic effects. While these properties may be attributable largely to elemicine, no studies on the psychopharmacological activity of pure elemicine or safrol have as yet been made**,**For hallucinating purposes, ground nutmeg is taken orally in large doses, usually several teaspoonfuls. The effects vary appreciably but are often characterized by distortion of perception of time and space, dizziness, tachycardia, dry mouth, headache, and occasionally visual halucinations .

Chapter Five

1.Ways hallucinogenic drugs affect the Central nervous system development .

Hallucinogens are a loosely defined group of compounds including LSD, N,N-dimethyltryptamines, mescaline, psilocybin/psilocin, and 2,5-dimethoxy-4-methamphetamine (DOM), which can evoke intense visual and emotional experiences. We are witnessing a renaissance of re- search interest in hallucinogens, driven by increasing awareness of their psychotherapeutic potential. As such, we now present a narrative review of the literature on hallucinogen binding in vitro and ex vivo, and the various molecular imaging studies with positron emission tomography (PET) or single photon emission computer tomography (SPECT). In general, molecular imaging can depict the uptake and binding distribution of labelled hallucinogenic compounds or their congeners in the brain, as was shown in an early PET study with N1-([11C]-methyl)-2-bromo-LSD ([11C]-MBL); displacement with the non-radioactive competitor ketanserin confirmed that the majority of [11C]-MBL specific binding was to serotonin 5-HT2A receptors. However, interactions at serotonin 5HT1A and other classes of receptors and pleotropic effects on second messenger pathways may contribute to the particular experiential phenomenologies of LSD and other hallucinogenic compounds. Other salient aspects of hallucinogen action include permeability to the blood–brain barrier, the rates of metabolism and elimination, and the formation of active metabolites. **(Oña, G & al., 2021).**

2. Mechanisms of action of specific hallucinogens molecules

2.1.Effector molecules of hallucinogenic developing drugs

2.1.1. Lysergic Acid Diethylamide

Swiss chemist Albert Hoffman first manufactured LSD in 1938. **(Hoffman, A.1979)**. but did not accidentally swallow an exact amount and discovered its properties until 5 years later, in 1943. In 1937, just 1 before LSD was first manufactured, Vit- Tory Espamer identified a substance from intestinal cells that caused smooth muscle contraction and named it undermine **(Das, S & al., 2016)** . For several years, Ertbamer and his colleagues studied the effects of amine intestines in different tissue systems, including the heart of slugs and the salivary gland of octopuses. In 1948, Maurice Rapport and Irvine Page at Cleveland Clinic isolated a substance of clotted cow blood with vascular-straightening properties and named it serotonin.

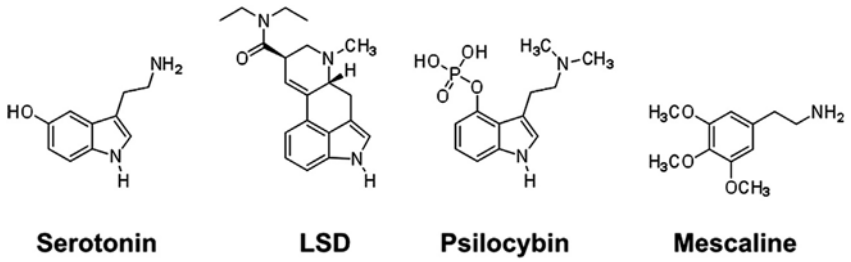


Figure 26 : Structures of classic hallucinogens. The structure of serotonin is shown compared to that of other classic hallucinogens.**(Berridge, M. J & al., 1973).**

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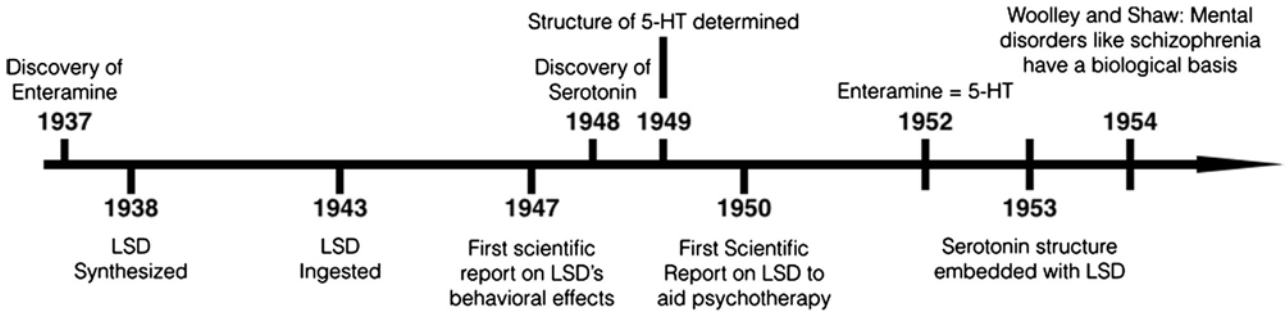


Figure 27 : Timeline of the discovery of serotonin (5-HT) and lysergic acid diethylamide (LSD). **(Berridge, M. J & al., 1973).**

The chemical composition of serotonin was clarified in 1949 and identified as 5-hydroxy-triptamine **(Rapport, 1949).** It was not until several years later, in 1952, that intestinal and serotonin were shown to be the same molecule. Shortly thereafter it was established that serotonin was present in the brain **(Twarog & Page, 1953).** Gadum reported in 1953 that the chemical composition of serotonin was embedded in the LSD structure and noted that because LSD affected the brain, where serotonin was also found, LSD may interact with serotonin systems . In fact, Gaddum found that LSD was able to prevent systolic effects of serotonin on mouse uterine tissue**. (Mohammad-Zadeh & al.,2008).** The extraordinary nature of the experiments triggered by hallucinogens naturally motivated scientists to look for a lower status than Psychopharmacology and working mechanisms. Hallucinogens belong to a variety of structural categories, including argoline, phenylethylamine and terptamine .

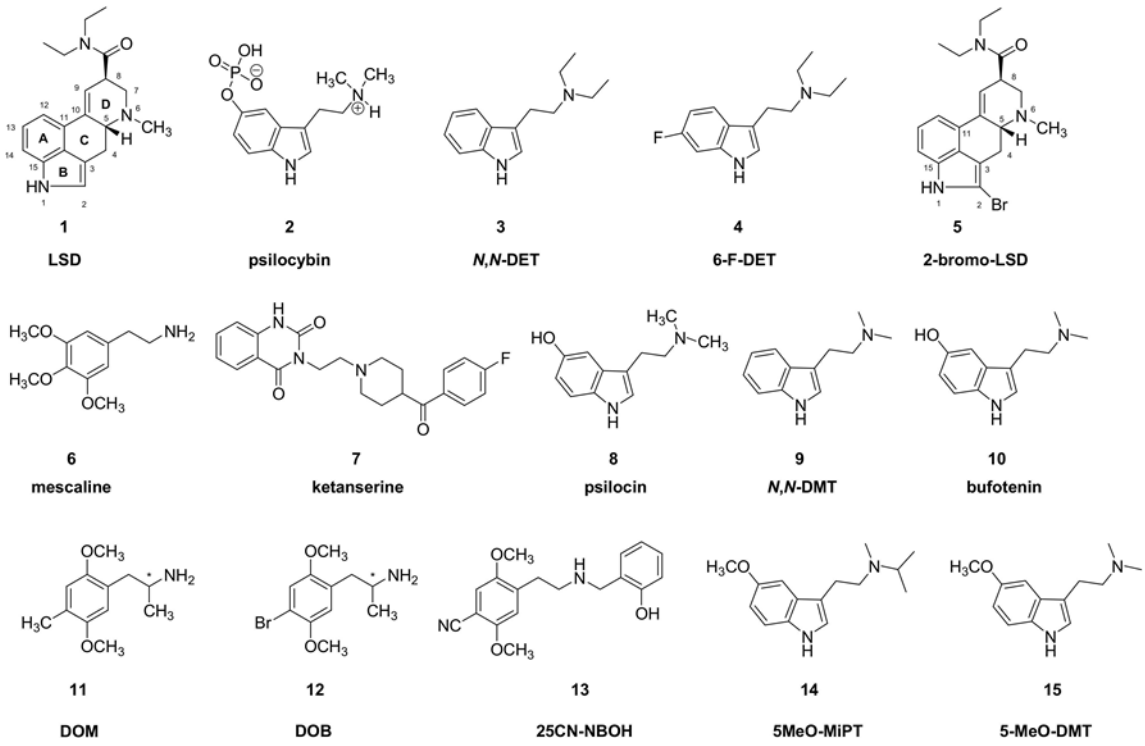


Figure28: Chemical structures of LSD and some classic hallucinogenic compounds—(*) indicates chira centers. **(Cumming, P & al., 2021).**

2.1.2. The Methoxy Phenylethylamines and Amphetamines

Phenethylamines (PA), together with preparation, terptamine (TA) and CA, possess stimulating and degrading effects, forming the category of so-called products, psychoactive molecules that promote empathy and emotion. PA are synthetic compounds commercially known as "party beans."

Shulgin, Sargent and Narango manufactured and tested a large number of methoxygenated phenylitlamines and amphetamines that have hallucinogenic activity in humans. 13 All these molecules consist of a level gasoline ring, replaced by a number of methoxy groups and an ethylamine group or isopropylamine. We'll start looking in the direction of methoxy groups. **(Zuba, D & al., 2013).**di-4,5-methoxyamphetamine contains methoxy groups at ring level; The ethylene chain is almost normal for ring level, anti-ring nitrogen atom. We portray a similarity associated with LSD consistent with these boundaries. In Table Atomic coordinates are given in picometres on a usurped coordinate system that is personally selected to associate with LSD for this formation of di-4,5-trimethoxy - (R) - amphetamine.

Table 08: Atomic coordinates in picometers of a model of the conformation of ,4,5-trmethoxyamphetamine.

ATOM	x	Y	Z	AT0M	X	y	Z
C1	70	121	0	NH3	247	247	145
C2	-70	121	0	CH3	35	317	211
C3	-140	0	0	O (2)	-142	243	0
C4	-70	-120	0	CH(2)	-285	223	0
C5	70	-120	0	O (4)	-142	-243	0
C6	140	0	0	CH(5)	285	-223	0
C7	147	255	0	O(5)	142	-243	0
C8	173	300	145	CH3 (5)	285	-223	0

2.1.3. Tryptamine

Tryptamines are naturally occurring alkaloids found in a variety of plants and life forms around the world and exist in >1500 natural varieties. The basic element of tryptamine is the indole structure and tryptamine itself is an endogenous amine found in the human brain. Serotonin and Melatonin are two essential tryptamines present as neurotransmitters in the brain. Tryptamines can be also produced either completely synthetically or semisynthetically. **(Fantegrossi, W. E & al., 2008).**

Tryptamines with hallucinogenic activity include the derivatives N,N-dimethyl, N,N-diethyl, 4-hydroxy N,N-dimethyl (psilocin), 4- phosphate N,N-dimethyl (psilocybin), and a methyl.2' Psilocybin is rapidly hydrolyzed to psilocin in ViVo**.(Karle, I. L & al., 1965) .**

As an example of this class of hallucinogens we shall discuss the conformation of psilocin, which has three structural parameters excluding hydrogen orientations :

the torsion angle C2-C3-C1O-C11; or the position of the a-carbon atom relative to the plane of the ring system ;the torsion angle C3-C11-C12-N; or the position of the nitrogen

atom relative to the torsion angle C10-C11-N-C12 or its equivalents; or the orientation of the nitrogen atom.

Dimethyltryptamine (DMT) is an active principle of various South American snuff, such as "COHOBA" and "YOPO." It has been produced synthetically for a number of years .Psilocybin and psilocin are found in at least 15 species of mushrooms ,so-called "magic mushrooms", belonging to the genera psilocybe, panaeolus, and conocybe.

LSD is fairly rigid, and that phenylethylamine tryptamine and derivatives contain a planar group and a flexible side chain which can take up several different conformations whose energies are not widely separated. Any one conformation relevant to a biological system would be stabilized relative to the others on interaction with an active site.

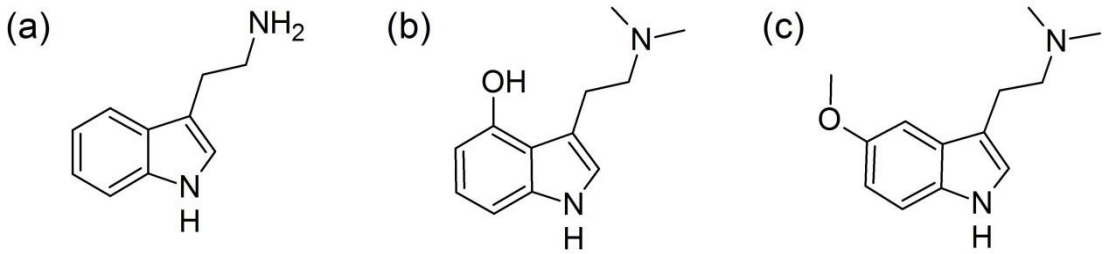


Figure 29 : Image showing the structure of Tryptamine derivatives.

(Berridge, M. J & al., 1973)

3. Molecular and functional studies of clinical hallucinogenic molecules from experimental studies

Despite the maturity of Radiochemistry and molecular imaging in recent years, there have been only a handful of PET or SPECT studies of radiation-marked hallucinogens, which have recently been used as an agonist 5-HT2A/2C N- (2 [11CH3O] - methoxybenzyl) -2.5-dimethoxy- 4-bromofine ethyl in addition to PET studies for targeted participation in neurotransmitters, there are a few studies on the effects of hallucinogenic compounds on cerebral ischemia ([15O] - water) or metabolism ([18F] - fluorodioxglucose/Fdg) There is still considerable scope for basic imaging research **. (González-Maeso, J & al., 2007).** Hallucinogens are a loosely defined group of compounds, including LSD, N, N-

dimethyltryptamines, mescaline, psilocybin/psilocin, 2. 5-dimethoxy-4-methamphetamine (DOM).

4. The nature of agonist-receptor interactions

there is evidence that both classes of hallucinogens produce their electrophysiological effects through a partial agonist action at 5-HT2 (particularly 5-HT2A) receptors. There is also evidence from biochemical **(Sanders-Bush & al., 1988)** and behavioral. **(Glennon 1990)** studies that the effects of halluci- nogens involve a partial agonist action at 5-HT2 receptors. Thus, 50 years after the discovery of 5-HT, the 5-HT hypothesis of the action of both indoleamine and phen- ethylamine hallucinogenic drugs can be reformulated in terms of specific 5-HT receptor subtypes, with a pri- mary focus on 5-HT2 receptors.

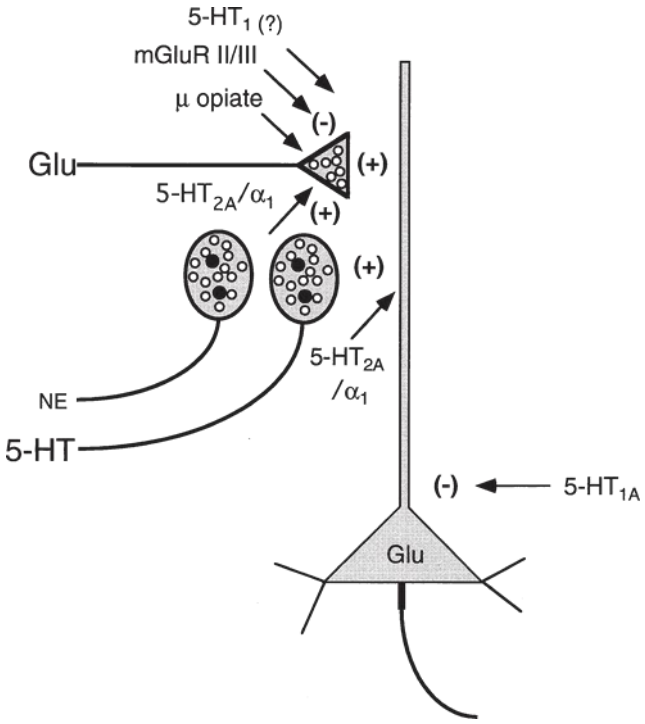


Figure 30 : Schematic diagram depicting 5-HT inputs (from the raphe nuclei) and nonadrenergic (NE) inputs (from the locus coeruleus) projecting to the vicinity of the apical den- drite of a layer V pyramidal cell in neocortex. **(Aghajanian, G. J & al., 1975).**

5-HT, acting via 5-HT_{2A} receptors, is shown to induce the release of glutamate from an excitatory nerve terminal (+); to a lesser extent, NE, acting via α_1 receptors, also induces glutamate release. Also shown are inhibitory modulators of 5-HT_{2A}- induced glutamate release: μ opiate, group II and III metabo- tropic glutamate (mGluR II/III), and as yet an

uncharacter- ized non-5-HT_{2A} receptor (possibly a 5–HT_1 subtype). In addition, excitatory (5-HT_{2A} and α_1) and inhibitory (5-HT_{1A}) postsynaptic effects of 5-HT and NE are shown.

5. Detection of laboratory-level hallucinogen binding sites

Although hallucinogenic research faces significant regulatory obstacles as a potential tool for treating these disorders and possibly others **(Heal, D. J & al., 2013),** we are here reviewing previous and more recent studies that focused on the effects of certain hallucinogens as therapeutic drugs Clinical studies conducted in the 1950s and 1960s suggest that hallucinogens, especially LSD, may serve as therapeutic drugs. Without noting the need for the main warning regarding the study of hallucinogens in preclinical models is the inability of currently available behavioural models to convincingly prove that rodents suffer from the effects of hallucinogens observed for human users. There are many animal models that can effectively distinguish nugin from non-halocenogen serotonic agonists **(Hanks & al., 2013)**. However, no behaviours have been identified in rodents caused by the effects of both serotonergic (e.g., LSD and psilocybin) and hallucinogenic drugs (e.g., Pencyclidine (PCP) and scopolamine), indicating that the models to be described below..

The results indicate the transmission of the frontal cortex in the effects of hallucinogens targeting 5-HT2A receptors. The effects of hallucinogens by the effects of 5-HT2A receptor regulated signal pathways in medium cortical neurons. An elegant experimental approach to recording signals from the 5-HT2A cortical pyramid receptors was found in multiple regions of the brain and is expressed and psychotic symptoms, such as the frontal cortex, abdominal region. **(Pazos, A & al., 1985).**Indicated that brain regions such as dorsal Ravi and the Serulius site may play a key role in the electrophysiological properties of The following studies specifically addressed the group of neurons responsible for the hallucinogenic receptor function.

Both LSD and the closely related nonhallucinogen 5-HT2A receptor agonist lisuride activate the same population of 5-HT2A receptors expressed in cortical pyramidal neurons. LSD stabilizes a distinct receptor conformation that has been proposed to be responsible for the cellular signaling events that lead to the neu- robehavioral responses observed. This does not occur with lisuride. The cellular and behavioral responses to LSD are absent in 5-HT2A-knockout mice (Htr2a−/−). Restoration of 5-HT2A receptor signaling capacity in cortical

pyramidal neurons of 5-HT2A-knockout mice (Htr2a−/−:Emx1-Cre+/−) rescues the cellular and behavioral effects of LSD **(Gonzalez-Maeso & al., 2007).**

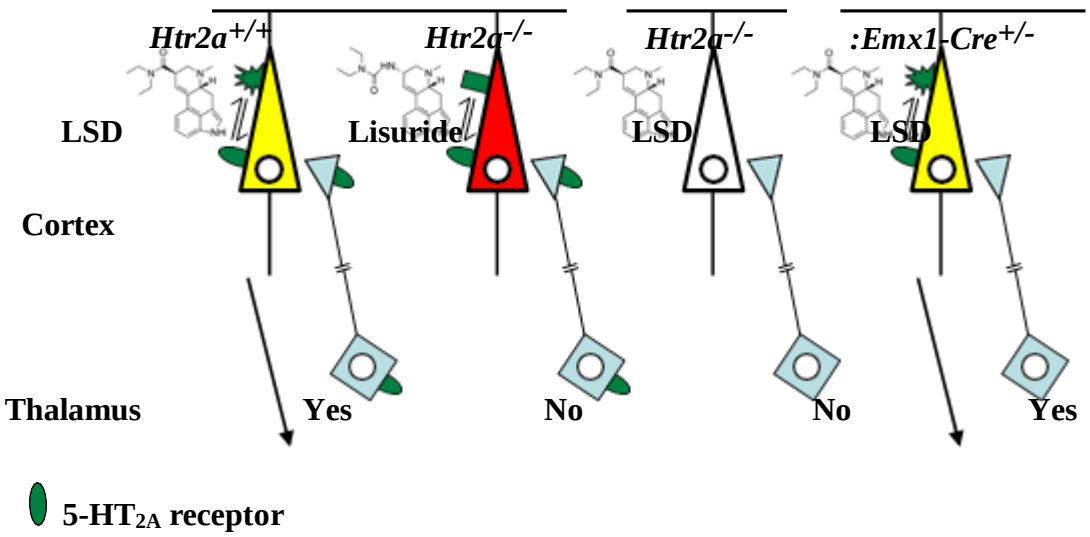


Figure 31 : Model of the molecular mechanisms and neuronal circuits underlying the behavioral responses induced by hallucinogens. **(Gonzalez-Maeso & al., 2007).**

5.1 Affinities of LSD at neuroreceptors in vitro

LSD (1, 100 µg) attained a maximal plasma concentration of 4 nM at two hours after oral administration in healthy volunteers, and declined thereafter with an approximately four hour half-life **.(Dolder, P. C & al., 2007) .**The subjective effects, both good and bad, closely tracked the plasma concentrations, as did physiological responses, such as heart rate and blood pressure increases. The metabolism of LSD is complex, but the predominant pathway in human involves microsomal formation of 2-oxo-3-hydroxy-LSD; whereas N-demethylation occurs in animals, this may not be an important pathway in humans **.(Libânio Osório Marta & al., 2019).**

Self-imaging studies of mice on MIL revealed that repeated doses with hallucinogenic MDMA triggered a significant reduction in the regulation of 5HT2-like receptors , which may be a sign of the phenomenon of carrying some hallucinogens. The specific correlation MIL**. (Son, H & al., 2019)** .in the mouse 'brain peaked at 45 minutes after injection, When the correlation ratio for the cerebellum was 4 in the frontal cortex and 2 in the scheme; The corresponding studies .LSD **(Cumming, P & al., 2021)**. observed a lower crust association and faster drift than the frontal cortex. In other live studies, ketancirin (7) triggered dose-dependent displacement .MIL in the mouse and cortex diagram, indicating that IC50 is about £30 g/kg ketancirin. **(Dos Santos, R. G & al., 2021).**

Table 09: Interaction of LSD and Phenethylamine Hallucinogens with 5-HT Receptor Subtypes **(Glennon 1990; Marek and Aghajanian 1996a).**

Receptor Subtype	LSD	Phenethylamines
5-HT_{1A}	+	—
5-HT_{1D}	+	—
5-HT2A/2C	+	+
5-HT_3	—	—
5-HT_4	—	?
5-HT_5	+	—
5-$HT_{6/7}$	+	—

5.2. Affinities of Hallucinogenic Phenylethylamines in Vitro

A series of phenylethyalamines in the Cimbi series showed Kiss in vitro against the binding of [3H]-MDL100907 ranging from 0.2 nM (Cimbi-31, 36) to 47 nM (Cimbi-88, 37); their receptor agonism was assessed from PI hydrolysis in GF62 cells overexpressing the 5-HT2A receptor. **(Ettrup, A & al., 2011)** . Furthermore, a series of nine structurally similar compounds of the Cimbi phenethylamine class had a ten-fold range in the affinity at 5HT2A sites and a 100-fold range in their ED50 for activation of IP hydrolysis .However, neither property predicted the specific binding (BPND) in brain, which ranged from 0.2 to 1.0. The best of the series with respect to specific signal and washout from cerebellum was [11C]-Cimbi- 36 **. (Aghajanian, G. J & al., 1975)** . [11C]-Cimbi-36 shows preferential uptake in

frontal cortical regions and relatively little uptake in the striatum, diencephalon and cerebellum .

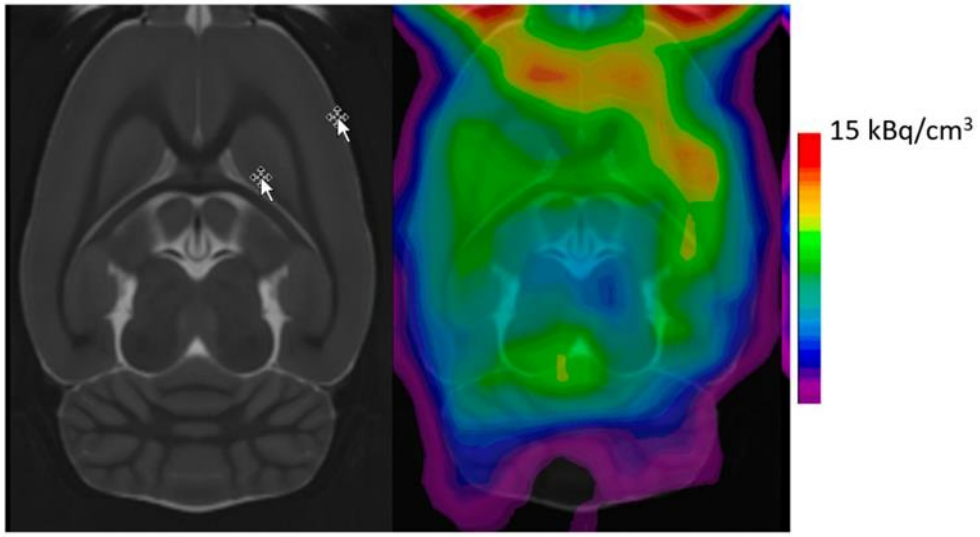


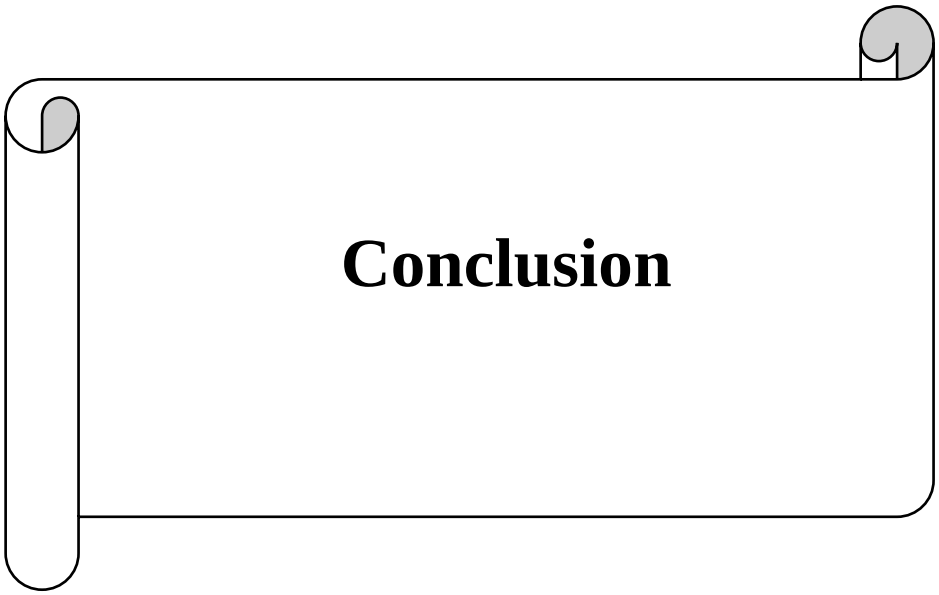
Figure 32 : [11C]-Cimbi-36 activity summed over the 45 min scan time in rat brain (right) overlaid on an MR template image in the horizontal plane (left). High activity in cortical regions, especially mPFC, moderate activity in striatal and hippocampal regions and low binding in cerebellum. **(Cumming, P& al., 2021).**

5.3.Affinities of Hallucinogenic Tryptamines in Vitro

Tryptamine substituted compounds are characterized by the rapid metabolism in vivo through the removal of methyl O by CYP2D6, and oxidation by MAO .**(Shen, H. W & al., 2010)**, so that the main metabolites of 5-MeO-DMT (15) in mouse urine are DMT-glucuronate and 5-methoxy and as discussed below in some detail, the importance of MA , remarkably, there is evidence that DMT may be an internal neurotransmitter. Studies of super-expulsion of the mouse brain indicated that DMT (9) was present in a neuronal cell part, along with its precursors, tryptamine**.(Christian, S. T & al., 1977) .**

DMT obtained a brain:blood partition ratio of about 5:1 after intraperitoneal injec- tion in the rat, but disappears rapidly from tissue and circulation due to metabolism. **(Cohen, I & al., 1972).** A planar scintigraphy study examined the biodistribution of radioactivity in rabbits following intravenous injection of 2iodo-DMT . The brain activity reached a peak about 30 s

after injection, when the brain:blood ratio was approximately unity in the olfactory bulb, thus indicating very fast passage across the blood–brain barrier. Remarkably, traces of activity remained in the olfactory bulb (but not elsewhere in the brain) for several days after administration; the authors suggested that this might reflect trapping in vesicles and noted that a rabbit study with 2-iodo-tryptamine showed no comparable retention in brain. They authors did not undertake any displacement studies to confirm specific binding, nor did they pretreat the rabbits with a monoamine oxidase (MAO) inhibitor, arguing that the intravenous route of administration avoided first pass metabolism in the liver**.(Berlowitz, I & al., 2019).**



Conclusion

Hallucinogen and non-hallucinogen 5-HT2A in the mouse's sensory bodily cortex, an area involved in cellular and behavioural responses to hallucinogenic drugs.Highlight that regulating individual signalling methods, such as protein coupling G, β-based signalling, or install phosphate accumulation, is a poor indicator of hallucinogenic activity often , These observations indicate that some unique responses generated by hallucinogens may depend on the exact subcellular environment defined for 5-HT2A receptors and the stoic measurement of medium signals in the neurons responsible for these effects. In addition, this response may result from the regulation of hallucinogens for more than one signal path.

Although it is difficult to determine the activity of many signalling pathways in brain tissue. So we relied on the precise identification of rapidly regulated genes as multidimensional neural signal reporters. Because gene expression is regulated by signal transmission methods, the tempting approach was to compare multiple signalling pathways affected by these two groups of drugs in complete animal models.

the cortical effects of hallucinogens result from their activity at 5-HT2A expressed by projected neurons on the cerebral cortex cortical neurons are unlikely to summarize the distinctive response signal to hallucinations observed in vivo. However, results similar to those obtained in vivo were obtained in the mice's physical, sensory cortex on the mice's crustacean primary farm **.(González-Maeso & al., 2007).** Thus, cells expressing 5-HT2A receptors showed stimulation of surface after exposure - certainly either LSD or R-lisuride. After exposure to LSD, 5-HT2A receptor Egr-2 coli in cultured cortical neurons. In conjunction with the results in vivo, these observations indicate that the 5-HT2A receptor is a key goal in identifying differentiated cellular and behavioral responses provoked by hallucinogens and non-halocenogens.

The latest figure shows the following results: ((−)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI), 1-(2,5-dimethoxy- 4-methylphenyl)-2-aminopropane (DOM), 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), mescaline, lysergic acid diethylamide (LSD), and psilocin) and nonhallucinogens (ergotamine, R-lisuride, and S-lisuride) in somatosensory cortex of wild-type (Htr2a+/+) and 5-HT2A-knockout (Htr2a−/−) mice. Note that c-Fos is induced by all 5-HT2A receptor agonists (hallucinogens and nonhallucinogens), whereas Egr-1 and Egr-2 are induced only by hallucinogens **(Hanks, J. B & al., 2016).**

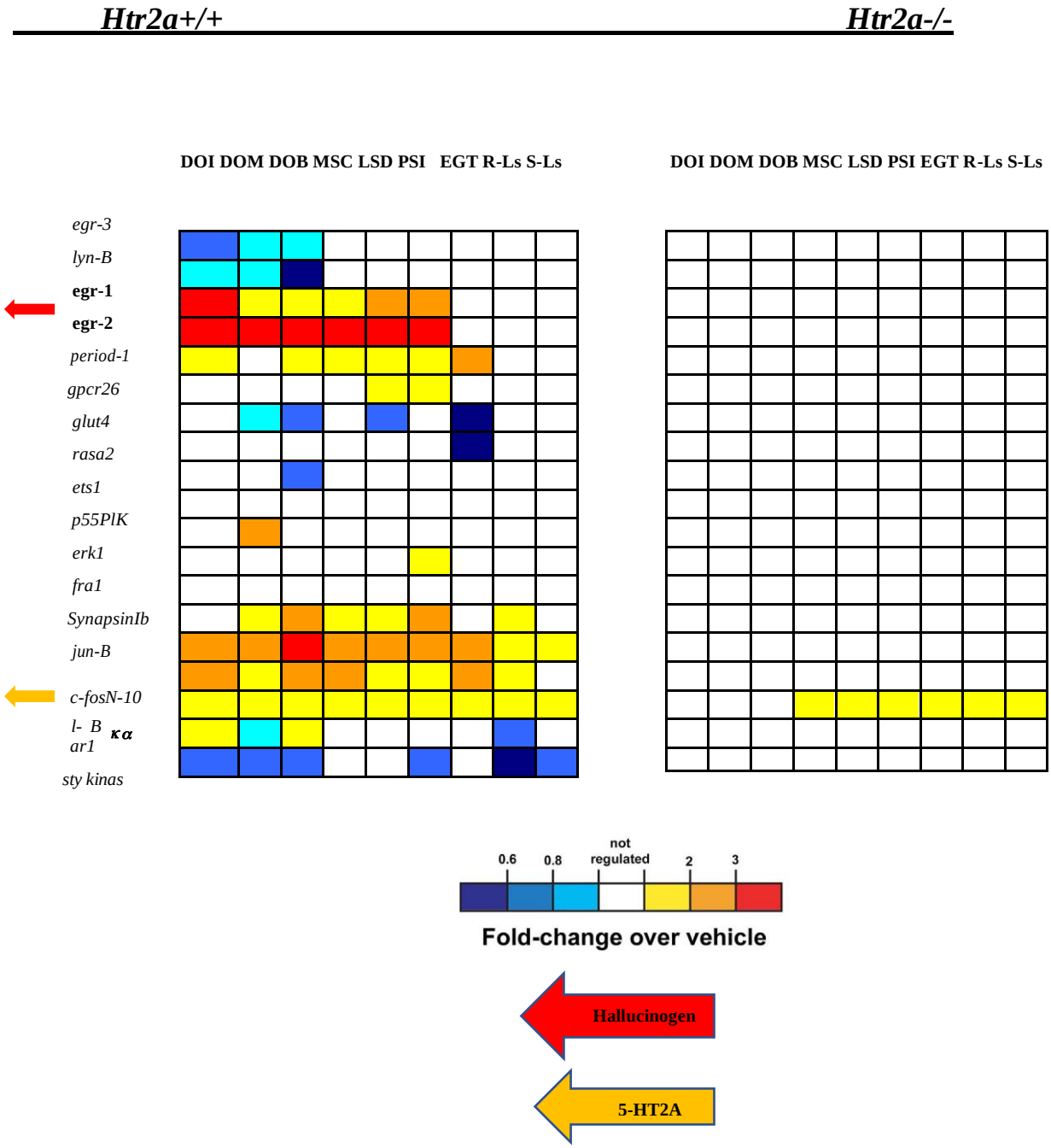


Figure 33 : Transcriptome fingerprint induced by hallucinogens.

(Hanks, J. B & al., 2016).

Hallucinogens may lead to negative reactions requiring the intervention of health and law enforcement professionals when taken in uncontrolled environments. However, research indicates the therapeutic potential of hallucinogenic compounds when managed under clinical protocols that maintain hospitals "ethical and clinical responsibilities."And how do the separate neurological procedures of hallucination genes, as described above, explain dramatic disorders in the cortical function produced by hallucinogenic genetic drugs.For example, enhancing sensory response to LC neurons, perhaps through their extensive cortical projections, may contribute to distinctive intentions - preparing certain types of cognitive experience supportive of hallucinations. In the cerebral cortex, enhancing the prolonged, delayed and asynchronous component of glutamaterial transmission by hallucinogens may be behind some of the cognitive and cognitive abnormalities produced by these drugs.

From the axes of the chapters of this topic, we can highlight the role of botany and its hallucinogenic molecules and their contribution to the field of medicine in the following points:

- Proof of copy fingerprint that can predict behavioral response to diverse 5-HT antibodies is highly relevant to the development of more specific therapeutic drugs.
- Hallucinogens activate 5-HT receptor-regulated signal pathways on cortical hormonal neurons.
- the results suggest that hallucinogens may serve as therapeutic drugs for treating severe psychiatric disorders such as alcoholism, obsessive compulsion and cluster headaches.
- Hallucinogens are used recreationally, and thus illustrating the mechanism by which these drugs stimulate their unique psychiatric effects is an important goal for drug use research.
- The main caveat regarding the study of hallucinogens in preclinical models is the inability of currently available behavioral models to convincingly prove that rodents suffer from the effects of hallucinogens observed to human users.

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