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Phytochemical profile of cannabis plant: A review

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Abstract
Cannabis plant is increasingly becoming a topic of public discussion. All efforts by United Nations Single Convention on Narcotic Drugs (UNODC) have triggered a major obstacle for cannabis to be seen for its medicinal potentials. However, over the years, illegal cannabis consumption has grown making users' cannabis dependent. Cannabis dependency affects the users' brain and body, initiating side effects which pose risk of survival, attacking the Central Nervous System, responsible for sanity and co-ordination. Cannabis contains more than 400 bioactive constituents worthy of investigation. Neurological disorder caused by cannabis dependency is associated with its primary constituent THC, tetrahydrocannabinol. This compound increases the dopamine level of the brain. This paper is expected to contribute a more rational approach involving the use of dopamine antagonist as a cure to cannabis dependency.

Keywords: Cannabis, tetrahydrocannabinol, neurological disorder, dopamine antagonist

Introduction
Plant *Cannabis sativa*, commonly referred to as ganja in Tamil is a medical plant that has strongly divided the research community. It can probably be said that Cannabis is the most controversial plant in the history of mankind. Based on history, it has potential to treat anything ranging from headache to neurological disorders and cancer. It is therefore interesting to know that after decades of research, its medicinal potential continues to be disputed.
Cannabis originated from Central Asia. It was used as food or medicine. Some religions were closely related with the properties of the cannabis plant. For example, in Hindu legend, cannabis is believed to be the favorite food of the god, Shiva, because of its tranquilizing properties. Today, Cannabis is the most commonly used psycho-active drug world-wide, together with coffee and tobacco. Over 160 million people are cannabis dependent and these numbers are still rising. [1] The commonly used term 'marijuana' or 'marihuana' traditionally describes the cannabis plant when used as a recreational drug leading to cannabis dependency and overdose. Marijuana dependency is associated with the negative effects and social impact of the drug.

Cannabis Constituents
Marijuana, the *Cannabis* plant and its products consist of different chemicals. More than 483 compounds involving various phyto-chemicals are present in marijuana. These active compounds include phyto-cannabiniods, Terpenes, steroids, and many others. [2] The term "cannabiniods" represents a group of C_{21}terpenophenolic compounds which are uniquely present in *Cannabis sativa* L. [3].

Phytochemical screening of marijuana
The qualitative and quantitative analyses of marijuana (*Cannabis sativa L.*) continue to be a significant task at most photochemical laboratories. The most common techniques utilized for these analyses are Gas Chromatography/Flame Ionization Detector and Gas Chromatography/Mass Spectroscopy, High Performance Liquid Chromatography, and High Performance Thin Layer Chromatography. Other methods of analysis include Solid Phase Micro Extraction technique (SPME). Stable Isotope Ration- Mass Spectrometry (IRMS) and DNA profiling. The applicability of capillary electro chromatography with photodiode array UV detection for the analysis of phyto-cannabinoids has been demonstrated.
Supercritical fluid chromatography coupled with atmospheric pressure chemical ionization/Mass Spectroscopy is characterized by shorter analysis times than Gas Chromatography or high-performance liquid chromatography and does not require derivatization [2].

Table 1: Cannabinoids of cannabis plant

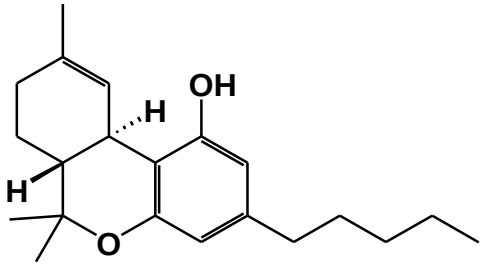
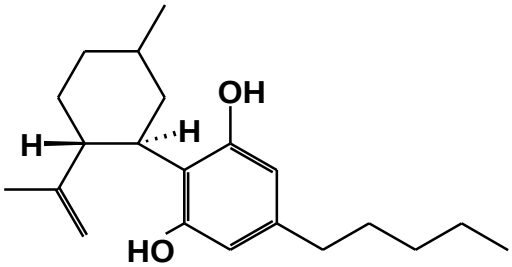
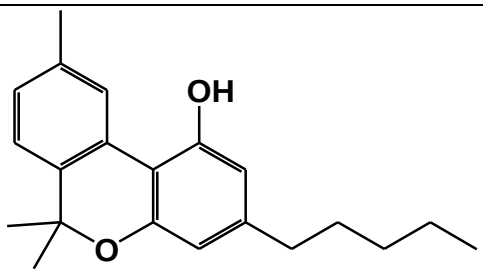
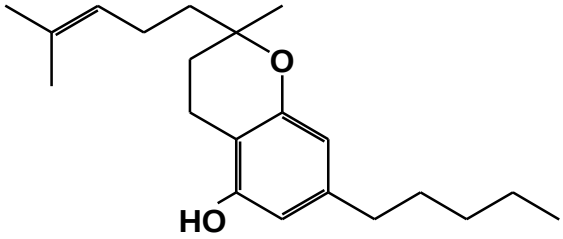
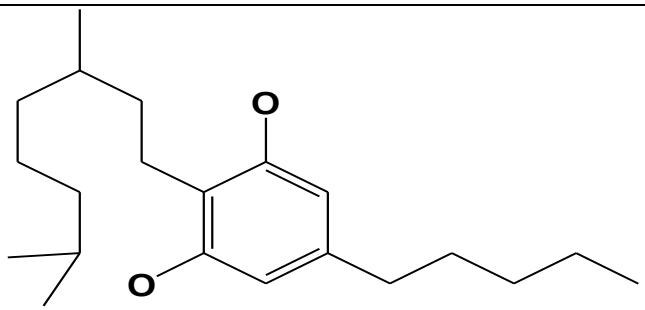
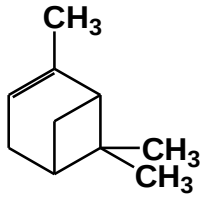
Phytoconstituents	Medicinal use	Structural formula
 THC- tetrahydrocannabinol	Antioxidant Analgesic Anti-inflammatory Ephoriant Antiemetic	$C_{21}H_{30}O_2$
 CBD- cannabidiol	Analgesic Antioxidant Anti-inflammatory Antipsychotic Anxiolytic Antispasmodic	$C_{21}H_{30}O_2$
 CBN- cannabinol	Antibiotic Sedative Oxidant	$C_{21}H_{26}O_2$
 CBC- cannabichromene	Antibiotic Anti-inflammatory Antifungal	$C_{21}H_{30}O_2$
 CBG- cannabigerol	Antibiotic Antifungal Anti-inflammatory	$C_{21}H_{32}O_2$

Table 2: Terpenoid essential oil compounds of cannabis

Phytoconstituents	Medicinal use	Structural formula
 α- pinene	Anti-inflammatory Stimulant Antibiotics Antineoplastic	$C_{10}H_{16}$

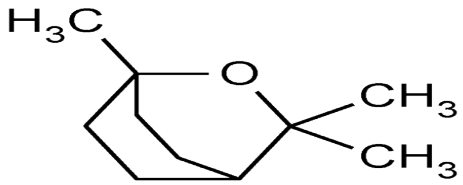
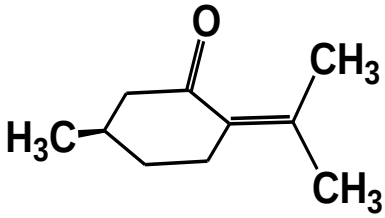
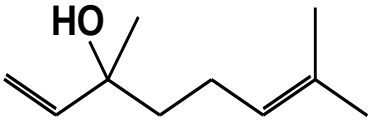
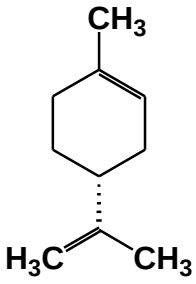
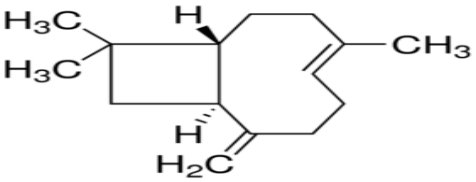
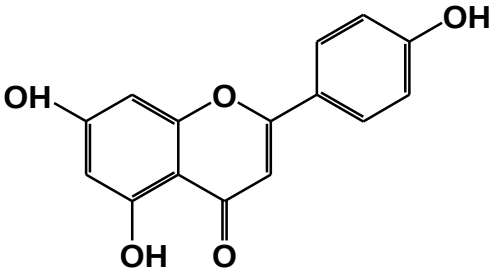
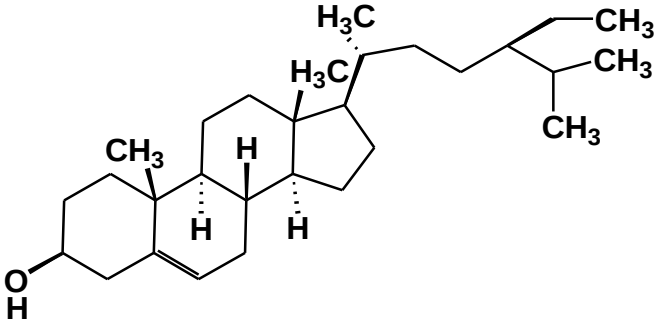
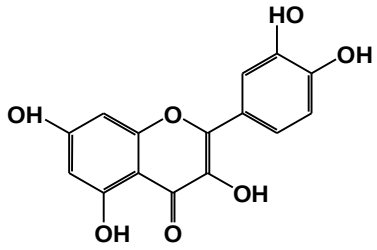
 1,8-cineole (eucalyptol)	Anti-inflammatory Antibiotics Antiviral Stimulant	$C_{10}H_{18}O$
 Pulegone	Sedative Antipyretic Memory booster	$C_{10}H_{16}O$
 Linalool	Sedative Antidepressant Anxiolytic	$C_{10}H_{18}O$
 d- limonene	Antidepressant Cannabinoid agonist Anti- mutagenic	$C_{10}H_{16}$
 β – caryophyllene	Anti-inflammatory Antimalarial	$C_{15}H_{24}$

Table 3: Flavonoid and Steroidal compounds of cannabis

Phytoconstituents	Medicinal use	Structural formula
 Apigenin	Anti-inflammatory Axiolytic Estrogenic	$C_{16}H_{10}O_5$
 β- sitosterol	Anti-inflammatory	$C_{29}H_{50}O$

 Quercetin	Antioxidant Antiviral Antineoplastic	$C_{15}H_{10}O_7$

The table below shows an illustration of the preliminary qualitative study of Marijuana in Nigeria, Africa. However, based on different growing conditions (e.g. amount of watering, grown without or with soil, i.e. indoor or outdoor grown, type of soil and fertilizer, etc.), the isotopic composition of the plants can be affected and thus discrimination may be limited [4].

Test for Alkaloids
Few drops of Dangendroff's reagents were added in 2 ml of petroleum ether crude leaf extract of cannabis in a test tube. The resultant mixture was observed for colour change usually orange to deep orange coloration.

Test for Saponin
10ml of distilled water were added to 2 ml of the petroleum ether crude leaf extract of cannabis in a test tube. It was shaken vigorously for 1 minute and allowed to stand for 30 seconds after which 3 drops of Olive Oil was added and observed for color change usually dark brown coloration.

Test for Tannins (Ferric Chloride test)
Using the ferric chloride test, tannin was determined by adding three drops of 10% ferric chloride ($FeCl_2$) in 2 ml petroleum ether crude leaf extract of Cannabis which was diluted with 4 ml of distilled water. The resultant mixture was observed for color change usually reddish precipitates formed.

Test for Flavonoid (Lead acetate test)
Flavonoid was tested for by adding 2 ml of 10% lead acetate solution in 2 ml of the petroleum ether crude leaf extract of Cannabis in a test tube plus 2 ml of 10% lead acetate solution. This was allowed to stand for 10 seconds after which the mixture was observed for color change usually yellowish coloration and precipitate formed.

Test for Cardiac Glucosides (Keller-Killiani test)
Cardiac Glycoside test was determined by adding 2 ml of glacial acetic acid and 1 drop of ferric chloride ($FeCl_2$) to 1 ml of the petroleum ether crude leaf extract of cannabis in a test tube. Finally, 1 ml of concentrated tetraoxosulphate (V1) acid (H_2SO_4) was carefully introduced in a slanting position down the side of the test tube and was observed for brown ring inter phase formation.

Test for Terpenes and Steroids (Burchard test)
Terpenes and Steriods were tested by adding 1 ml of anhydrous acetic acid to 2 ml of the petroleum ether crude leaf extract of cannabis in a test tube. Concentrated tetraoxosulphate (V1) acid (H_2SO_4) was carefully added down the side of the test tube and was observed for a reddish color change and inters phase formation.

Test for Balsams
Balsams were determined by adding 2 ml of alcohol ferric chloride to 2 ml of the petroleum ether crude leaf extract of cannabis in a test tube. The mixture was then warmed over a Bunsen flame for 5 seconds and was observed for reddish brown color change.

Test for Volatile Oils
Volatile oils were determined by adding 0.1ml of dilute sodium hydroxide (NaOH) followed by 0.5ml of hydrochloric acid (HCL) to 2 ml of the petroleum ether crude leaf extract of cannabis in a test tube. This was then allowed to stand for 5 seconds and observed for a light blue color change and precipitate formed.

Test for Resins
Resins were determined by adding 2 ml of acetic anhydride to 2 ml of the petroleum ether crude leaf extract of cannabis in a test tube. Three drops of concentrated tetraoxosulphate (V1) acid, (H_2SO_4) was carefully added and then observed for a violet color change.

Table 4: Preliminary Quantitative Analysis of Marijuana in Nigeria, Africa

Phytochemicals	Presence/absence	Colour	Reagent
Alkaloid	+++	Orange	Dragendoff's
Saponin	-		
Flavonoids	++	Light Yellow	Lead acetate
Tannins	-		
Cardiac glycosides	+++	Reddish Brown	Keller-Killani
Balsam	-		
Phenols	-		
Terpenes and Steroids	+++	Reddish Brown	Burchard
Resins	+++	Violet	
Volatile oil	-		

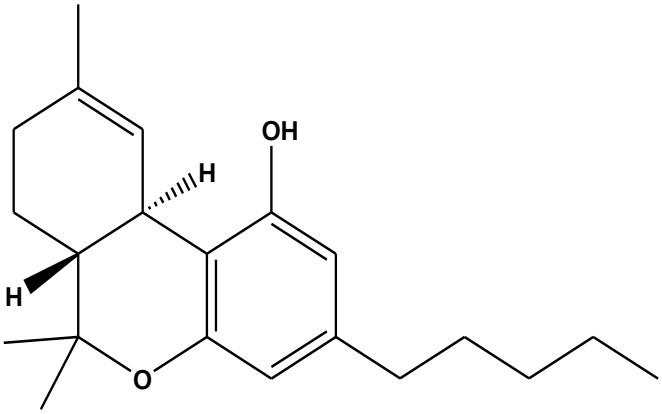
+++High presence; ++ moderate presence; -Absence

Biological study of cannabis
There are two methods for biological study of any compound; they are *In vivo* and *In vitro* analysis. It is important to also look into the i*n vitro* and the *in vivo* efficacy of non-psychoactive cannabidiol in neuroblastoma. Neuroblastoma is one of the most common solid cancers in children. [5] Two active compounds namely THC and CBD are administered along with the drug.
Therefore, experimentation is done to determine the effects of those compounds for viability, invasiveness, cell cycle distribution, and programmed cell death in human Neuroblastoma SK-N-SH cells using Annexin V Assay, Caspase Assay and Invasion Assay.
The results obtained in the *in vitro* studies can be summarized as follows: Both molecules—and CBD in particular—reduced the viability of Neuroblastoma cells. The effect of CBD seemed to be mediated by apoptotic cell death, as demonstrated by morphology changes, accumulation of sub-G1 cells, annexin V assay, and increased expression of

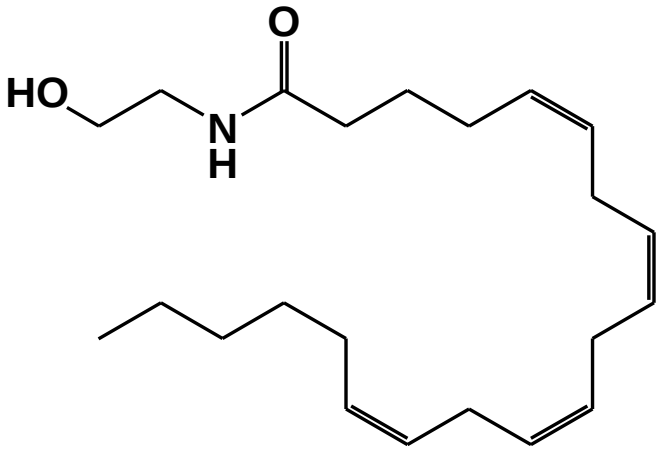
cleaved caspase assay. The invasiveness of Neuroblastoma cell was also reduced with Neuroblastoma treatment. Both compounds have antitumourigenic activity *in vitro* and impeded the growth of tumour xenographs *in vivo*. Of the two cannabinoids tested, CBD was the most active.

Cannabis dependency and the human brain

However, the dependency of cannabis affects the body [6], mostly the central nervous system (brain and spinal cord) [7]. The main chemical constituent responsible for these is THC (tetrahydrocanabinol) [8]. Behavioral [9] and pharmacological studies [10] indicate that both acute and chronic exposure to cannabiniods is associated with impairments in range of cognitive processes [11]. Specifically, the chemical tetrahydrocannabinol (THC) resembles a neuro - transmitter in the brain, an endocannabinoid compound that is released when neurons are firing [12]. The neurons temporarily become unresponsive after firing to prevent overreacting or being too dominant. This allows the brain to function in a calm and controlled manner, but cannabinoids interrupt this approach in some parts of the brain. Instead, they remove the refractory period of neurons that are already active, and cause thoughts, imagination and perception to utterly magnify itself.



Tetrahydrocannabinol



Anandamide

Anandamide is a molecule which acts as a neuro-transmitter; it has a structure very similar to that of tetrahydrocannabinol, the active constituent of cannabis. It is a messenger molecule that plays a role in many bodily activities, including appetite, memory, pain, depression, and fertility. Anandamide has a long hydrocarbon tail which makes it soluble in fat and allows it to easily slip across the blood-brain barrier. Its 3-dimensional shape strongly resembles that of THC. However, THC is a relatively robust molecule, whereas anandamide is fragile and breaks down rapidly in the body. That is why anandamide does not produce a strong intoxication. [13] Interestingly, cannabiniods also affect the level of dopamine and norepinephrine in the brain, often leading to a sense of euphoria, relaxation, pain modulation, and experience of trance; though sometimes causing anxiety. Since, cannabis is said to increase the dopamine level of the brain, it is important to produce dopamine antagonists for the treatment and cure of cannabis dependency.

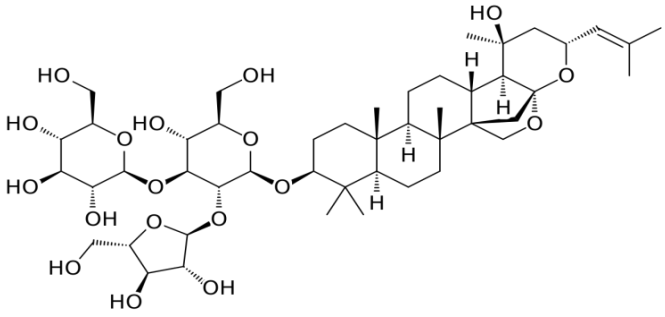
Antidote for cannabis dependency

The major health risk caused by cannabis overdose is classified into two, psychological effect which has to do with mood, perception, cognition and psychomotor performance. The second is the systematic effect that involves the cardio-vascular, respiratory and other organs of the body.

No medications are currently available to treat cannabis dependency, but chemical dependency counseling support is considered to be effective through therapy and motivation. Consistent research study may lead to new medications that help prevent relapse, ease withdrawal symptoms and block the negative effects of cannabis. The effect of overdose of marijuana is connected to addictive behaviors, and mental disorders. Since overdose of marijuana contributes to high level dopamine in the brain, dopamine antagonist could be used to safely normalize or reduce high level dopamine in mentally healthy people.

Bacopa

Bacopa (*Bacopa monnieri*) Indian pennywort is a very popular herb used in the Indian Ayurvedic tradition of medicine where it is also known as "Brahmi", [14]It is a popular brain-boosting supplement that enhances memory, learning, and concentration which is good majorly for age-related mental declination. It is also a mood enhancer that reduces both anxiety and depression. It contains triterpenoid saponins known as bacosides.



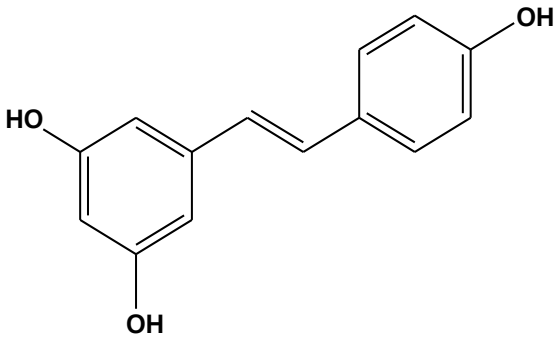
Bacoside

Bacopa regulates levels of dopamine, serotonin, and GABA (gamma-Aminobutyric acid)by moving production up and down as needed [15]. This potential ability of bacopa is so unique. Therefore, it is an excellent all-purpose herb for achieving and maintaining overall CNS and body balance.

White Mulberry

White mulberry *(MorusAlba)* is a small ornamental tree native to China which is widely cultivated to feed silkworms. White mulberry supplements are used mainly to regulate blood sugar, control appetite, and help with weight loss, but

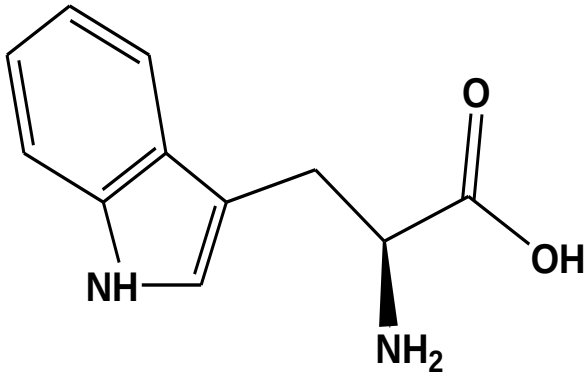
they also effectively regulate excess dopamine [16]. One of the bioactive compounds in White mulberry is Stilbenoid, a flavonoid compound.



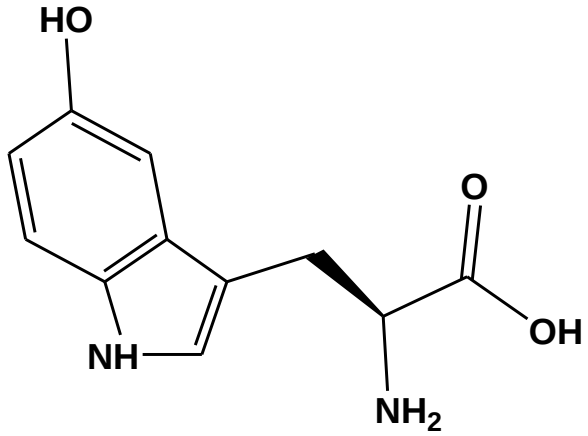
Stilbenoid

Tryptophan and 5-HTP

Tryptophan, an amino acid found in animal protein sources, is the precursor of the neurotransmitter serotonin. It is also the precursor to another amino acid, 5-HTP. 5-HTP (5-Hydroxytryptophan) is a popular supplement usually taken for insomnia, anxiety, and depression. Both 5-HTP and tryptophan are supplements and both reduce excess dopamine [17].



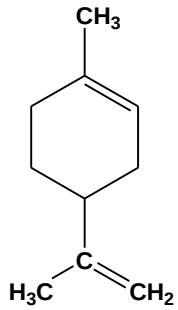
Tryptophan



5- HTP

Lemon Essential Oil

This is the simplest and most pleasant way to normalize dopamine by the use of lemon essential oil (*Citrus limon*). Lemon oil is enriched with about 67.6 percent of Limonene constituent. Inhaling lemon oil vapors offers anti-anxiety and antidepressant effects. Limonene speeds up the turnover of dopamine in the hippocampus. [18]



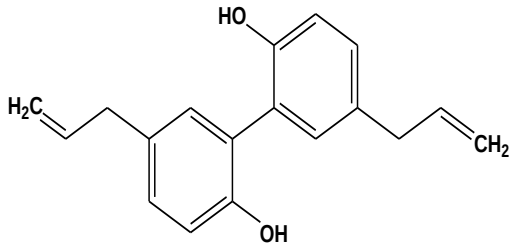
Limonene

Noni Fruit

Noni fruit (*Morindacitrifolia*) comes from a small evergreen tree that grows in volcanic soils of the South Pacific. In traditional medicine, noni is considered a natural cure-all and is used to treat colds, flu, diabetes, and high blood pressure, as well as depression and anxiety. It is undoubtedly a nutritional powerhouse and it also happens to lower dopamine [19]. The key active ingredients in noni are alkaloids called proxeroxine (a precursor to xeronine) which is yet to be identified by conventional researchers.

Magnolia Bark

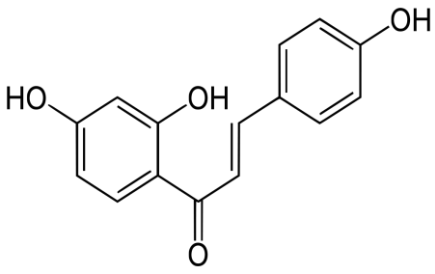
Magnolia bark (*Magnolia officinalis*) with bioactive constituent called magnolol is a bitter herb used in traditional Chinese medicine for digestive disorders and to treat asthma. It is a relaxant which is good for stress relief, anxiety, and depression. It protects the brain from oxidation and inflammation [20]. This dopamine inhibitor is available in capsules, as a liquid extract or dried powder, or as a tea that goes by the name Houpo tea.



Magnolol

Licorice Root

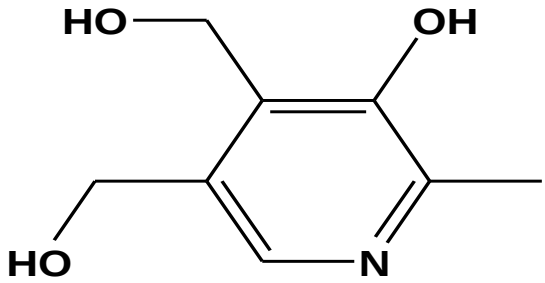
Licorice root (*Glycyrrhizaglabra*) is mostly known as a popular flavoring used in candy. Its botanical name is Glycyrrhiza which means “sweet root.” But, it also has a long history of medicinal use by both traditional Chinese and Ayurvedic healing practices. Licorice supplements are recently used mainly to treat digestive disorders and ulcers. Licorice has many bioactive compounds including isoliquiritigenin which blocks the production of dopamine and is being studied as a possible antidote to cocaine abuse [21].



Isoliguiritigenin

Vitamin B6 (Pyridoxine)

Scientists have proven with evidence that an excess of dopamine can cause vitamin B6 deficiency [22]. This means that vitamin B6 is a cofactor required and highly essential for the syntheses of dopamine. This also makes it an antidote for overdose which could be taken as a supplement to reduce dopamine activity in the brain.



Pyridoxine

Conclusion

Cannabis has the potential to evolve into a useful and much more needed medicine but due to its high level of dependency, it is seriously obstructed by its classification as a dangerous narcotic. At international level, there are not several reports based on the study of this plant from different continents of the world. The National Academic Press (2017) illustrated the several therapeutic health effects of cannabis on the body and also its effect on disease control and cure with possible side effects that can be derived from an overdose or misuse of drug molecule. Presently in India, only few articles are written on this medicinal plant for its therapeutic potential. Nevertheless, there are articles based on the analytical methods and properties of drug extracts as an alternative to Opioid drugs.

The pharmaceutical application of marijuana cannot be overemphasized. Marijuana has been used for centuries as herbal remedies for the treatment of many illnesses. Though not scientifically proven, medical marijuana can be used to treat a number of different conditions, such as alzheimer's disease, appetite loss, cancer, crohn's disease, eating disorders such as anorexia, epilepsy, glaucoma, mental health conditions like schizophrenia and posttraumatic stress disorder (PTSD), multiple sclerosis, muscle spasms, nausea and pain. A few small studies have reported the benefit of cannabis to treat cancer especially side effects of chemotherapy. The FDA has also approved dronabinol (Marinol, Syndros) and nabilone (Cesamet), man-made cannabinoids, to treat these symptoms when other nausea medications do not work. Some studies have found that smoked marijuana can ease cancer-related pain. It binds to cannabinoid receptors in the brain and other parts of the body. Therefore, the isolation of purified bio-active compounds derived from or based on the cannabis plant, will be a more promising therapeutic approach to its health benefit than use of the whole marijuana plant or its crude extracts. The legal use of cannabis for its medicinal properties will help substitute for prescription drugs which poses high risk of side effects caused by opioid drugs. The legality of cannabis and professional guidance on dosing, routes of delivery and adequate standardization or quality control promotes medicinal usage of herbal plant. With regards to possible side effects caused by cannabis plant due to its recreational use, this paper also suggests the possible dopamine antagonists from plant sources as useful antidotes to neurological disorder caused by cannabis dependency.

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