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A review on isolation of active constituents of some crude drugs

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I. INTRODUCTION

The isolation of bioactive compounds such as ephedrine, morphine, curcumin, eergometrine and diosgenin is crucial in both pharmaceutical and nutraceutical industries. Ephedrine, an alkaloid derived from Ephedra species, is well-known for its stimulant and bronchodilator properties. Morphine, a potent opioid alkaloid extracted from the opium poppy, is essential in pain management and is widely studied for its analgesic and addictive properties. Curcumin, the active component of turmeric, is recognized for its anti-inflammatory and antioxidant effects, contributing to its use in treating various ailments. Ergometrine, derived from the ergot fungus, has significant applications in obstetrics due to its uterotonic effects. Diosgenin, a steroidal saponin found in Dioscorea species, serves as a precursor in the synthesis of various steroid hormones and is noted for its potential health benefits.

The isolation process typically involves in the extraction techniques such as solvent extraction, chromatography and recrystallization. These methods aim to purify the target compounds from complex matrices, ensuring high purity and efficacy. Advanced techniques like high-performance liquid chromatography (HPLC) and mass spectrometry are often employed to confirm the identity and purity of the isolated compounds.

Understanding the isolation and characterization of these compounds is fundamental for developing therapeutic agents and supplements, improving quality control and advancing research in medicinal chemistry. This process is not only ensuring the availability of these valuable substances but also facilitates the exploration of their full therapeutic potential.

1. Isolation of Ephedrine from Ephedra

Ephedrine

Ephedrine is a natural alkaloidal compound derived from the plant belongs to the genus Ephedra. It has stimulant effects on the nervous system and is used primarily as a bronchodilator (to ease breathing) and as a decongestant. In the past, it was also used as a weight loss supplement and as a performance-enhancing drug in athletics due to its stimulant properties.

Biological source: it consists of the dried young stem of Ephedra geradiana&Ephedra nebrodensis belonging to **family**Gnetaceae

Physical Properties

Appearance: Ephedrine typically appears as fine, white or off-white crystals or powder.

Solubility: It is soluble in water and ethanol (alcohol), slightly soluble in chloroform and ether.

Melting Point: The melting point of ephedrine hydrochloride (a common salt form) is approximately 187-188°C (368-370°F).

Odor: It is odorless or may have a faint odor depending on purity.

Taste: Ephedrine has a bitter taste.

Density: The density of ephedrine varies depending on its form and crystalline structure, but it generally has a density higher than water.

Stability: It is stable under normal storage conditions but can degrade upon exposure to light, air or high temperatures.

Chemical properties

Basicity: Ephedrine is a weak base due to the presence of the amino group ($-NH_2$). In solution, it can exist in different forms depending on the pH of the environment. In acidic conditions, it predominantly exists in its protonated form (e.g., ephedrine hydrochloride), which enhances its solubility and stability.

Reactivity: Ephedrine is stable under normal conditions but can undergo chemical reactions such as oxidation and reduction, depending on the chemical environment. It is susceptible to degradation when exposed to light, heat or acidic conditions over prolonged periods.

Salt Formation: Ephedrine can form salts with various acids, such as hydrochloric acid (ephedrine hydrochloride) or sulfuric acid. These salts are

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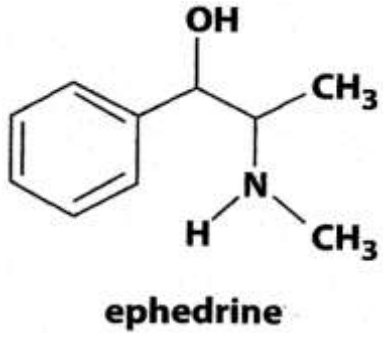
often used in pharmaceutical formulations to enhance stability, solubility and bioavailability

Chemical structure



ephedrine

Therapeutic uses: Anti-asthma, Anti diabetes, Anti hyperlipidaemia, Anti neuroinflammatory, Anti Alzheimer activity, Anti rheumatoid arthritis, Anti-cancer, Anti-oxidant, Anti-microbial activity and CNS stimulant.

Isolation of Ephedrine

Plant Material: Ephedrine can be extracted from plants such as Ephedra geradiana, Ephedra nebrodensis,Ephedrasinica or Ephedraequisetina, which contain high concentrations of the alkaloid.

Grinding: The plant material (stems, leaves) contain ephedrine isground into a fine powder to increase surface area.

Extraction: The powdered plant material is then soaked or macerated in a suitable solvent like ethanol or methanol. This step allows the ephedrine alkaloids to dissolve into the solvent.

Filtration: After extraction, it is filtered to remove any solid plant materials in the solvent.

Concentration: The solvent is evaporated under reduced pressure (using a rotary evaporator) to concentrate the crude extract.

Purification: The concentrated extract undergoes further purification steps to isolate ephedrine:

Chromatography: Techniques such as column chromatography or thin-layer chromatography (TLC) can be employed to separate ephedrine from other alkaloids and impurities.

Recrystallization: Ephedrine can be crystallized out from the solvent by cooling or by adding a suitable antisolvent, followed by filtration and drying to obtain pure crystals.

Characterization: The isolated ephedrine crystals are typically characterized using spectroscopic techniques like NMR (Nuclear Magnetic Resonance) and mass spectrometry to confirm their identity and purity.

Storage: Finally, the purified ephedrine is stored in appropriate conditions (usually dry and away from light) until further use or analysis.

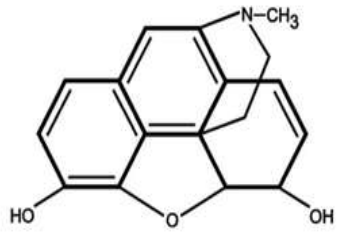
2. Isolation of Morphine from Opium

Morphine

It is a potent analgesic (pain-relieving) drug that belongs to the class of opioids. It is derived from the opium poppy plant Papaver Somniferumbelonging to family Papaveraceaeand is one of the oldest known painkillers used by Humans. Morphine works by binding to opioid receptors in the brain and spinal cord, thereby reducing the perception of pain. It is commonly used to treat severe pain, such as that experienced after surgery, during cancer or in palliative care for terminal illnesses. The characteristics of morphine include its ability to relieve pain significantly and induce feelings of euphoria and sedation.

Physical properties Morphine is usually found as a white crystalline powder. It is also available in the form of morphine sulphate and morphine hydrochloride salts, which are more soluble in water. The pKa values for morphine are around 8.21 and 9.85, indicating the presence of two basic functional groups (the amine and the phenolic hydroxyl group). The properties of morphine contribute to pharmacological profile, including its ability to cross the blood-brain barrier and bind to opioid receptors in the central nervous system. Melting Point of morphine range between 255°C to 256°C (491°F to 493°F), density approximately1.34 g/cm³, poorly soluble in water, soluble in ethanol and readily soluble in chloroform.

Structure of morphine It has a complex polycyclic structure with five membered rings have the chemical formula$C_{17}H_{19}NO_3$. The molecular weight of morphine is 285.34 g/mol.



Therapeutic Uses: Morphine, the active constituent of opium is responsible for its action. Opium is an analgesic, hypnotic or narcotic, unlike many other hypnotics, it acts mainly on sensory nerve cells of cerebrum. It checks excessive peristalsis and contracts the pupil of eye. Effective

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for relief of pain, depressant action on respiratory centre and cough.
Morphine can be administered orally, intravenously (IV), intramuscularly (IM), subcutaneously (SC), depending on the clinical situation. Common side effects include drowsiness, constipation, nausea, vomiting and respiratory depression. It can also cause tolerance, dependence and addiction with prolonged use. It is available in various forms including Tablets, capsules, injections and as part of patient-controlled analgesia (PCA) systems in hospitals. Due to its potential for abuse and addiction, the production, distribution, and use of morphine are strictly regulated. It is available only through prescription from licensed healthcare providers.

Isolation of Morphine
Materials required: Raw opium, Distilled water, Acid (e.g., acetic acid), Base (e.g., ammonia), Organic solvent (e.g., chloroform, ethanol), Filtration apparatus, Evaporation equipment
Procedure for isolation of Morphine
Extraction of Alkaloids: Dissolve the raw opium in distilled water to create anaqueous solution. Acidify the solution using acetic acid to ensure all alkaloids are in the salt form.
Filtration: Filter the solution to remove insoluble materials and impurities. The filtrate contains the alkaloids in the aqueous phase.
Basification: Add a base, such as ammonia, to the filtrate to convert the alkaloids into their free base form. This process precipitates the alkaloids out of the solution.
Re-extract with organic Solvent: Extract the precipitated alkaloids using anorganic solvent like chloroform. The organic layer will contain the free basealkaloids, including morphine.
Evaporation: Evaporate the organic solvent under reduced pressureto obtain a crude mixture of alkaloids
Purification: Dissolve the crude alkaloid mixture in a small amountof ethanol. Morphine can be selectively crystallized out by cooling the solution. Further purification may be achieved through recrystallization.
Recrystallization: Recrystallize the morphine from ethanol or any other suitable solvent to achieve high purity.

3. Isolation of Curcumin from Curcuma Longa (Turmeric)
Curcumin

Curcumin (diferuloylmethane), a low-molecular weight member of the curcuminoid class of compounds, is a bright yellow chemical produced by plants of the Curcuma longa species. It is the principal curcuminoid found in turmeric, a yellow Indian spice and member of the ginger family, Zingiberaceae.

Physical properties of Curcumin
Color and Appearance: Curcumin is a bright yellow-orange pigment that gives its distinctive color. It is typically found as a crystalline powder.
Solubility: Curcumin is practically insoluble in water but soluble in organic solvents such as ethanol and dimethyl sulfoxide (DMSO).
Melting Point: The melting point of curcumin is around 183 °C (361 °F).
Odor and Taste: Curcumin has a mild, earthy aroma and a slightly bitter taste.
Stability: It is stable in acidic and neutral conditions but can degrade in alkaline environments and when exposed to light.
UV-Visible absorption: Curcumin exhibits strong absorption in the visible region of the electromagnetic spectrum, with a peak absorption wavelength around 420 nm.
Crystal Structure: Curcumin molecules can form different crystal structures depending on the conditions of crystallization, affecting its properties such as solubility and bioavailability

Chemical properties of Curcumin
Chemical Structure: Curcumin is a polyphenolic compound and belongs toa group of compounds known as curcuminoids. Its chemical structure consists of two aromatic rings connected by a seven-carbon linker with two methoxy groups and two phenolic hydroxyl groups (-OH) attached.
Hydrophobicity: Curcumin is highly hydrophobic, meaning it does not dissolve well in water but dissolves readily in organic solvents such as ethanol, acetone and chloroform.
Tautomerism: Curcumin exhibits tautomerism, meaning it can exist in different forms (keto-enol tautomerism). The predominant form in solution is the enol form, which is more stable and bioactive.
Acidity and Basicity: Curcumin is a weak acid and can undergo ionization under certain conditions, influencing its solubility and chemical behavior in different environments.
Chemical Stability: Curcumin is relatively stable under acidic and neutral conditions but can degrade in alkaline environments and when exposed to light and heat. This degradation can affect its biological activity and bioavailability.
Reactivity: Curcumin has been found to exhibit antioxidant properties due to its ability to donate

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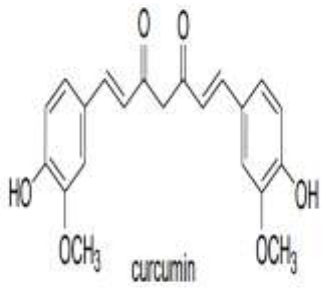
hydrogen atoms or electrons, thereby neutralizing free radicals and reactive oxygen species.

Complexation and Chelation: Curcumin can form complexes with metal ions, which can influence its biological activity and stability.

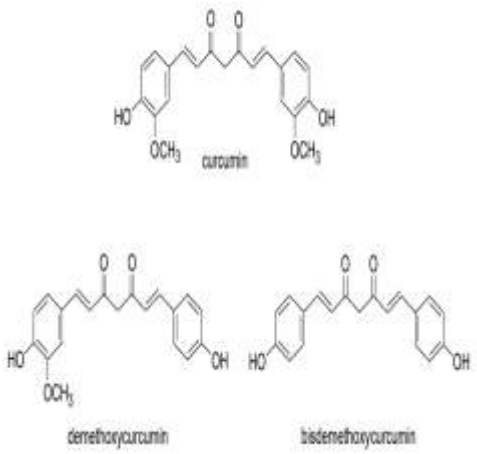
Interaction with Proteins: Curcumin can interact with various proteins and enzymes, affecting their structure and function, which contributes to its diverse biological effects.

Reaction with Biological Molecules: Curcumin can react with nucleophiles such as thiols (e.g., cysteine residues in proteins), which can lead to the formation of covalent adducts and modify protein function

Chemical structure



Chemical structure of 3 major contents in Curcumin



Isolation of Curcumin

Requirements:

The solvents used for the extraction of curcumin from Curcuma Longacomprise acetone, ethyl acetone, ethanol, methanol and isopropanol. To obtain flavor-free curcumin, it has been used to extract the essential oil from raw turmeric powder or turmeric oleoresin. A good yield of deodorized turmeric was produced following hydro-distillation method.

Method

Isolation of natural bioactive compounds generally involve a series of steps; selection of the plant component, cleaning and subsequent drying followed by extraction and purification of the desired compound.The various extraction methods available are generally categorized as traditional methods, such as Soxhlet extraction.Modern techniques, involving ultrasound assisted extraction, microwaveassisted extraction, super critical fluid extractions and even with ionic liquids.Post isolation, the bioactive compounds are identified using various chromatographic techniques, such as thin-layer. Curcumin is extracted from the rhizome of the turmeric plant. Generally, it is the powdered sample of turmeric which provides the highest extraction yield. In a typical procedure, hexane and acetone are used to extract the curcumin in the powder form. The choice of a suitable solvent also plays a critical role in the extraction process. Extraction with ethanol at 35 ^{o}C generally provides the highest curcumin extraction yield (72%) compared to solvents such as acetone, methanol and ethyl acetate. Various modern methods of extraction of curcumin have now been explored. Subcritical solvent extraction of curcumin using water/ethanol mixture (50:50 v/v) at high temperatures provided an extraction yield of almost 14%. According to the procedure, isolation of curcumin using column chromatography first involves the trituration of the crude extracted sample with hexane followed by dissolving in minimum amount of dichloromethane-methanol. Solvent ratio (99:1 v/v) and loading onto a column packed silica gel. Elution of the column was done with the same solvent. TLC analysis of the various fractions show the presence of all three major components of turmeric, of which the least polar colored component was determined to be curcumin.

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4. Isolation of Ergometrine from Ergot (Claviceps Purpurea)

Ergometrinee

Ergometrine is the natural alkaloid of Claviceps purpurea that grows on rye,grains, also known as ergonovine and sold under the brand name Ergot rate. Ergot is a fungus that infects rye and other grains. Ergometrine is produced as a secondary metabolite by Claviceps purpurea.

Physical Properties

Appearance: Externally, it is dark violet to black and it is internally whitish or pinkish white

Solubility: It is sparingly soluble in water and ethanol and practically insoluble in ether.

Melting Point: The melting point of ergometrine is approximately 181-184°C.

Odor: Disagreeable and faint

Taste:unpleasant

Stability: Ergometrine is stable under normal storage conditions when protected from light and moisture.

Chemical Properties

Ergometrine is a basic alkaloid due to the presence of an amine group and it can form salts with acids.It can undergo chemical reactionssuch as oxidation, reduction and derivatization.Ergometrine contains several chiral centers, making it a molecule that can exist in different stereoisomeric forms.It increases the amplitude and frequency of uterine contractions and uterine tone which causes the delay of uterine blood flow and mainly acts on myometrium

Therapeutical Uses

Management of Postpartum Hemorrhage (PPH): Ergometrine is often used to prevent or treat excessive bleeding after childbirth (postpartum hemorrhage) and it helps by causing uterine contractions, which can reduce bleeding.

Induction of Labor: It may be used to induce labor when necessary. Its ability to stimulate uterine contractions can help to initiate labor in pregnant women.

Treatment of Migraines: It has been historically used in the treatment of migraines, particularly those associated with vascular components. It acts on blood vessels in the brain, causing constriction, which can help to alleviate migraine symptoms.

Diagnostic Testing: It is sometimes used in diagnostic testing, such as the ergonovine test, to provoke coronary artery spasm in patients suspected of having variant angina

Isolation of Ergometrine

Step 1: To set up the ergot culture, grow Claviceps purpurea on agar to drive.Rye or some other grain susceptible to natural infection by this fungus is a good choice as medium.

Step 2: Allow the fungus to grow and produce ergot alkaloids in the form of secondary metabolites.

Step 3: Producethe sclerotia (ergot bodies) from the infected grains.

Step 4: Grinding the ergot bodies to fine powder that was harvested, which allows to increase surface area

Step 5: Solvent extraction using suitable solvents like ethanol or Methanol. This helps to dissolve ergometrine and other useful alkaloids present in the Ergot.

Step 6: Extract was filtered to eliminate solid particulates and to obtain crude extract solution

Step 7: Concentrate crude extract under reduced pressure to evaporate off the solvent and leave behind and residue containing ergometrine.

Purification: Purify the crude extract of ergometrine by chromatography processes (for example: column-chromatography, HPLC) to isolate other alkaloids and impurities. Recrystallize with suitable solvents to get pure Ergometrine.

Characterization: The characterization of the isolated ergometrine is done by using different analytical techniques like NMR, Mass and IR spectroscopic methods for its identification as well as purity evaluations in comparison to an authentic sample.In pharmaceutical purpose the ergometrine is prepared in suitable dosage forms such as tablet, injection or solution

5. Isolation of diosgenin from dioscorea

Diosgenin: Diosgenin is a naturally occurring steroidal sapogenin found in plants such as wild yam (Dioscorea species).It is a well-known steroidal sapogenin present abundantly in medicinal herbs such as Rhizoma polgonati, Smilax china and Trigonella foenum-graecum.It serves as a precursor molecule for the synthesis of various steroid hormones, including progesterone and corticosteroids.Besides being used as steroidal drug, it has high potential and interest in the treatment of various types of disorders like cancer, hypercholesterolemia, inflammation and several types of infection.Numerous studies have reported that Diosgenin is useful in prevention and treatment of neurological diseases.Diosgenin itself does not exhibit hormonal activity in humans but is used industrially as a starting material for the semi synthesis of steroid drugs like cortisone,

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pregnenedione and progesterone.Recently, Diosgenin was identified as a novel hit for α-glucosidase inhibitory principle from various extracts of Dioscoreabulbifera. Further Diosgenin was isolated and was found to exert >80% inhibition of crude murine intestinal α-glucosidase activity.

Physical Properties

Diosgenin is a solid compound,typically appears as white or off-white crystalline powder. The melting point of Diosgenin is around 204-208°C. It is practically insoluble in water but soluble in organic solvent such as ethanol, chloroform and acetone. Diosgenin itself is odorless. It is used as a precursor for the synthesis of various steroid hormones and other bioactive compounds.

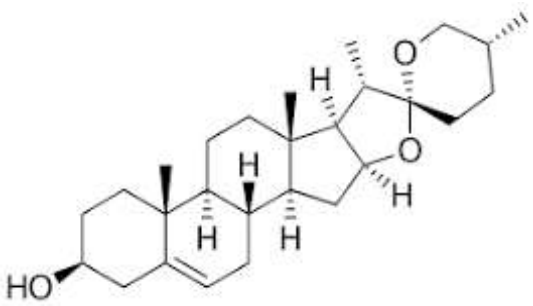
Chemical Properties

Diosgenin is naturally occurring steroidal sapogenin found in various plant, particularly in the tubers of Dioscorea species (wild yam). It possesses several chemical properties that are of interest: -

1) Steroidal structure: Diosgenin has a steroidal like structure with a spirostan skeleton. It is a precursor molecule in the synthesis of corticosteroids, sex hormones (such as progesterone) and other steroids.
2) Functional groups: Diosgenin contains several functional groups including hydroxyl (OH) group and a ketone group (C=O) which contribute to its reactivity in chemical reaction
3) Biosynthesis: It is biosynthesized from cholesterol and phytosterols in plants and can be converted into various steroidal hormones in human body.
4) Biological activity: Diosgenin exhibits various biological activities including anti-inflammatory, antioxidant, anticancer and hypercholesterolemic effects. These properties make it a subject of interest in pharmacology and medicine.
5) Chemical reactivity: Chemically, Diosgenin can undergo modification such as oxidation, reduction and acetylation, leading to derivatives with potentially altered biological activities or improved pharmacological properties.

Chemical Structure

Chemical formula: $C_{27}H_{42}O_{3,}$ Chemical structure is characterized steroid nucleus with hydroxyl group at C-3 and a double bond between C-5 and C-6, along with other substituents. The structure can be represented as: -



Isolation of Diosgenin

The isolation of Diosgenin through acid hydrolysis involves several steps to ensure the efficient extraction of this valuable steroidal saponin.

Sample Preparation

Source Material: Diosgenin is typically extracted from Dioscorea species (wild yam), which are rich in Diosgenin. The plant material should be dried and ground into a fine powder to increase the surface area for the extraction.

Extraction of Saponins

Initial Extraction: The powdered plant material is subjected to an initial extraction using a suitable solvent like ethanol or methanol. This step extracts the saponins, including Diosgenin, from the plant matrix.

Filtration: The solvent is filtered to remove solid particles, leaving behind a saponin-rich solution.

Acid Hydrolysis

The filtered solution is concentrated to remove the solvent, and the resulting residue is dissolved in an aqueous acidic solution, typically using dilute sulphuric acid ($H_2 SO_4$) or hydrochloric acid (HCl).The acidic solution is heated under reflux conditions. During this process, the saponins are hydrolysed into their component sugars and aglycones, with Diosgenin being the aglycone of interest. This reaction usually occurs at temperatures around 70-90°C and can take several hours.The hydrolysis reaction is monitored to ensure complete conversion of saponins into Diosgenin. Thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC) can be used to check the progress.

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Separation of Diosgenin

After hydrolysis, the acidic solution is neutralized using a base, such as sodium hydroxide (NaOH), to adjust the pH to a neutral range.Diosgenin is then extracted using an organic solvent like ethyl acetate or chloroform. The organic layer containing Diosgenin is separated from the aqueous layer.

Purification: The organic layer is concentrated and subjected to further purification techniques, such as column chromatography, to isolate pure Diosgenin.

Recrystallization: For further purification, Diosgenin can be recrystallized from a suitable solvent system to obtain high-purity Diosgenin.

Characterization

The isolated Diosgenin is characterized using techniques such as HPLC, TLC, or mass spectrometry to confirm its identity and purity.Further analysis might include nuclear magnetic resonance (NMR) spectroscopy to determine the structure of the Diosgenin.

Uses of Diosgenin

General Uses

Nutritional Supplements: Diosgenin is often included in dietary supplements, particularly those marketed for women's health, due to its role in hormone synthesis and potential to alleviate symptoms of menopause and premenstrual syndrome (PMS).

Cosmetics and Skincare: It is used in the cosmetics industry for its potential skin benefits, including anti-aging properties, moisturizing effects and skin elasticity improvement.

Therapeutic Uses

Hormone Replacement Therapy (HRT): Diosgenin is used as a precursor for the synthesis of various steroid hormones, including oestrogen and progesterone, which are used in HRT for menopausal symptoms.

Contraceptives: As a precursor to hormones like progesterone, Diosgenin plays a role in the production of oral contraceptives.

Anti-Inflammatory: Diosgenin exhibits significant anti-inflammatory effects, making it useful in the treatment of inflammatory conditions such as arthritis, asthma and inflammatory bowel disease (IBD).

Anti-Diabetic Effects: Research indicates that Diosgenin may help to regulate blood glucose levels and improve insulin sensitivity, making it a potential candidate for diabetes management.

Cardioprotective Effects: Diosgenin has been found to possess cardioprotective properties, including the reduction of cholesterol levels, improvement of lipid profiles and prevention of atherosclerosis.

Neuroprotective Effects: It may have neuroprotective effects, potentially benefiting conditions such as Alzheimer's disease by reducing oxidative stress and inflammation in neural tissues.

Pharmaceutical Uses

Synthesis of Steroid Hormones: Diosgenin is used in the synthesis of corticosteroids such as cortisone, hydrocortisone, and prednisone, which are used to treat inflammatory and autoimmune diseases, allergies and asthma. Diosgenin serves as a precursor for the production of estrogens (such as estradiol) and progestins (such as progesterone), which are used in oral contraceptives, hormone replacement therapy (HRT) for menopausal symptoms, and in treatments for menstrual disorders.

II. CONCLUSION

In conclusion, the isolation of ephedrine, morphine, curcumin, eergometrine, and diosgenin underscores the importance of extracting and purifying bioactive compounds to harness their therapeutic and medicinal properties. Each compound plays a unique role in medical and pharmaceutical applications: ephedrine for its stimulant effects, morphine for pain management, curcumin for its anti-inflammatory benefits, eergometrine for its uterotonic properties, and diosgenin as a precursor for steroid synthesis.

The successful isolation and characterization of these compounds rely on meticulous extraction and purification techniques, including solvent extraction, chromatography and advanced analytical methods like HPLC and mass spectrometry. These processes ensure the compounds' purity and efficacy, which is crucial for their application in drug development and therapeutic use.

Overall, the ability to isolate and study these bioactive compounds not only enhances our understanding of their mechanisms and potential health benefits but also contributes significantly to advancing medical science and improving patient care. The ongoing research and development in this field promise continued innovation and refinement in the use of these compounds for therapeutic purposes.

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