Review Article

Herbal anesthetic agents: An overview on sources, uses and future perspectives

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Abstract

Herbal folk drugs are progressively using in both western and Chinese societies. This is partly attributed to the supposed limitations of scientific medicine in the cure and control of chronic diseases. Such as herbal anesthetics treatment refers to plants which are used for their anesthetic properties. A large range of plants have been found to have analgesic or anesthetic property like coca for local anesthetic effect and valerian for general anesthetic effect. Consequently anesthetics can be used as analgesics to reduce pain but analgesics can't be used as anesthetics. Herbal folk anesthetics plants refer to herbs which are used for their anesthetic properties. A large range of plants have been reported to have analgesic or anesthetic effects, e.g. Coca, Clove, Cinchona, Dhatura, Jasmine and many more for local anesthetic effect and Valerian for general anesthetic effect. Their pharmacological diversity reflects the diverse neurochemistry and neurophysiology of pain and analgesia system in the nervous system. They have become an essential part of our medical treatment and these lead to the improvement of similar drugs with better clinical properties. This article covered some of the herbs which have been using as anesthetics along with their biological and geographical source, chemical composition, mechanism of action, and their evaluation.

***Keywords*:** Anesthetics, Herbs, Mechanism of action, sensitivity

Introduction

Herbs are annual, biennial or perennial seed-producing soft-stem plants that exhibit medicinal or aromatic and antioxidant properties (Charde et al., 2011). Historically, herbs have also been used to produce anesthesia. Dioscorides the Greek military physician described the drinking of mandrake by patients to cause insensibility during surgery. He used the word anesthesia for first time. Hua Tao, the Chinese physician and surgeon prescribed the herbal anesthetic mafesian with wine to render patients unconscious before performing operations (Cheng et al., 2002; Tripathi et al., 2008).

Anesthesia word comes from American and British English, is the process of blocking the sensitivity of pain and other sensations. It comes from the roots a "without" and aestnetos, "perceptible able feel" (Wyk et al., 2004).

Pain is used to refer to the local subjective phenomena associated with injury and suffering, nociception more specifically refers to the aspect of sensory transmission. Nociception is the more correct term for the experimental study of pain because it is objectively measured through behavior in animals and human alike e.g. withdrawal reflexes, verbal ratings. While anesthesia refers to blocking of all type of sensations, analgesia refers to the specific blocking of the pain, leaving other types of cutaneous senses (e.g. touch, pressure, temperature) intact. Local anesthesia refers to local blockade of never conduction whereas general anesthesia involves inducing deep unconsciousness with a depressant drug (Ebadi et al., 2007).

Cocaine, the first local anesthetic, originates from a specific plant alkaloid and the widely used intravenous anesthetic propofol shares the partial structure and pharmacological mechanism with certain plant terpenoids. The anesthetic adjunct morphine and the injectable muscle relaxant d-tubocurarine were also derived from opium poppy and the arrow poison curare prepared with vine plants, respectively (Fabricant et al., 2001).

For discovering drug candidates, plants of interest are screened for the presence of bioactive components and

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should be proper standardization (Bajaj et al., 2012; Mehta et al 2018; Sharma et al., 2013), phytochemicals responsible for the bioactivity are isolated, their molecular structures are identified, and then the original structures of phytochemicals may be semi-synthetically modified to enhance the activity or reduce the toxicity. In particular, a research strategy based on the pharmacological mechanism is very effective to obtain phytochemical lead compounds for anesthetics and anesthesia-related drugs.

This paper reviews different classes of phytochemicals with the significant anesthetic activity and their characteristic molecular structures from the point of view of well-known modes of anesthetic action, that is, the mechanistic interactions with ion channels, receptors and lipid membranes. The review focuses on terpenoids, alkaloids and flavonoids because they have been frequently reported to possess local anesthetic, general anesthetic, antinociceptive, analgesic or sedative property. Besides these phytochemicals, plants are able to produce anesthetic ethylene and vinyl ether especially under stress. Although these stress hormones were previously applied to inhalational anesthesia, they are infrequently used today due to toxicity and degradation during storage. Therefore, such phytochemical alkenes and ethers are not included in this review. Clinical applicability and implication of the relevant terpenoids, alkaloids and flavonoids are discussed by referring to animal in vivo experiments and human pre-clinical trials with them (Hironori et al., 2017).

Properties of ideal anesthetic

1. For the patient- Pleasant, non irritating, not cause nausea or vomiting, Induction and recovery fast.

2. For the surgeon – Adequate analgesia, immobility, muscle relaxation, non-inflammable, non-explosive.

3. For the anesthetics – Administration should easy, controllable and versatile.

Toxicity of anesthetics

1. The majority of reaction is due to over dosage Transient CNS stimulation followed by CNS and cardiovascular depression may occur.

2. Very profound CNS stimulation may lead to convulsion.

3. Rarely systemic allergic reaction may occur and topical sensitization may lead to dermatitis on the fingers of dentists who repeatedly come in contact with the drug.

4. The squealed of spinal anesthesia are hypotension due to blockade of sympathetic vasoconstrictor fibers. Higher the level of spinal anesthesia more intense is the hypertension. Trauma of lumbar puncture may cause transient headache. Spinal cord or nerve root damage may also occur[11]. Following herbal plants have been reported which showed anesthetic activity like as (Ley et al., 2006; Vogel et al., 2002).

Medicinal plants reported for anesthetic property

***Aconitum ferox* wall. ex ser. (Ranunculaceae)**

It is commonly called Indian Aconite. Chiefly chemical constituents are found in plant root, diterpenoid alkaloids**.** It has been used as catalyst, anodyne, thermogenic, anti-inflammatory, diaphoretic, expectorant, carminative, anti-ageing, enhance semen quantity, skin disease, flatulence, gout, cholera, increase appetite, asthma, paralysis, Sedative, antirheumatic, topically-anesthetic, analgesic, antitussive and antidiarrhoeal etc (Khare et al., 2007).

***Aconitum chasmanthum* (Ranunculaceae)**

It is commonly known Indian Napellus. The chemical constituents are found like mesaconitine, hypaconitine, 1.2%- acetylacoitine, lappaconitine (diterpenoid-ester alkaloids), benzaconine, benzoylaconine. The dried root uses as analgesic, anodyne, diaphoretic, diuretic, irritant and sedative. The root is a rich source of bio-active alkaloids, containing about 3%. This is a poisonous plant and should only be used with extreme care and under the supervision of a qualified practitioner, Sedative, Anesthetic, cardiotoxin and interacts with antiarrhythmics, antihypertensives (Bello-Ramírez et al., 2004; Yinglan Zhao et al., 2010),

***Anacardium occidentale* Linn (Anacardiaceae)**

It is locally known as cashew Nut. It is containing 45% fat and 20% protein flavonoids, mainly glycosides of quercetin and kaempferol, and hydroxybenzoic acid. The bark contains a balsam-containing anacardic acid, anacardol, cardol, ginkgo, and contains about 39% anacardic acid, a mixture of alkyl salicylic acid derivatives possess antioxidant, antibacterial, antiviral, antifungal, anti-tyrosinase and anti-quorum sensing activities. Methyl gallate isolated from cashew leaves showed potent anti-quorum sensing properties. Other pharmacological properties of cashew leaves include cytotoxic, hypoglycaemic, hypolipidemic, anticholesterolemic, anti-ulcerogenic, anti-hypertensive, analgesic bactericidal, fungicidal, vermicidal and protozoicidal hypotensive and anesthetic and anti-inflammatory activities. These bioactivities affirm that cashew leaves have medicinal values, and confer their traditional uses as food and medicine (Sehgal et al., 2001).

***Anacyclus pyrethrum* DC (Compositae)**

It is locally called Asteraceae Spanish, Pellitory, Pyrethrum Root. The plant root contains anacycline, isobutylamide, inulin and a trace of essential oil Mild Anaesthetics, Insulin-

dependent diabetes mellitus, decreased the plasma glucose and serum cholesterol levels after oral administration for 3-6 weeks. It has been identified to have properties of a sialagogue, to treat tongue paralysis, throat muscles, epilepsy, and rheumatism, aphrodisiac, and toothache reliever. The cortical portion of the root contains about 5% of the acrid compound called pyrethrin (pellitorine), which is responsible for the various medicinal values of this plant, especially its local anesthetic activity. sciatica, paralysis, hemiplegia and amenorrhoea (Annalakshmi et al. 2012).

***Aquillaria malaccensis* (Thymelaeaceae)**

The major compounds identified were 4-phenyl-2-butanone (32.1%), jinkoh-eremol (6.5%) and alpha-guaiene (5.8%), while the major compounds in the commercial oil were alpha-guaiene (10.3%), caryophellene oxide (8.6%), and eudesmol (3.2%). Useful for nervous system disorders, nervine, sedative, and refrigerant for heart disorder. Antimicrobial, anesthetic, analgesic, and showed positive effect on central nervous (Okugawa eta la., 1993; Gunasekera et al., 1981; Chen et al., 2012).

***Ceropegia juncea* Roxb. (Asclepiadaceae)**

It is called Bellagada. The chief chemical constituents are found such as pyridine alkaloid, cerpegin, together with a triterpene, lupeol. It has been reported promising hepatoprotective, antipyretic, analgesic, local anesthetic, anti-ulcer, mast-cell stabilizing, hypotensive activities Tranquilizing, hypotensive, hepatoprotective, antiulcer, antipyretic and topically-anaesthetic (Binish et al., 2018).

***Cinchona officinalis, C. calisaya, C. ledgeriana*. (Rubiaceae)**

It is commonly called Quinine; its bark contains alkaloids quinine, quinidine; cinchonine; cinchonidine and other alkaloids, quinamine, javanine. The leaves contain quercetin, kaempferol and avicularin Antimalarial. It has been used as local and anesthetic activity due to (i) Quinine and its derivatives, when brought in contact with sensory nerves, produce local anesthesia, this is used clinically in the form of the more soluble and less irritant double salts, especially quinine urea hydrochloride. (ii) The anesthesia is more lasting than with other local anesthetic, it may persist for several days. This is indeed to necrosis of the axis cylinders and sheaths, with subsequent regeneration. The concentration above 0.25% sometimes produces irritation, edema, and above 1%there may be sloughing. (iii) Its employment has therefore greatly diminished, although some clinicians fears as exaggerated. Antiarrhythmi, cardiac tonic, Mild Aneasthetic, Also prescribed in amoebic dysentery, jaundice, atonic dyspepsia, night cramps febrifuge, astringent, orexigenic and sapasmolytic (Hironori et al., 2017; Yan et al., 2016; Nadkarni et a., 1976).

***Datura innoxia* Mill (Solanaceae)**

It is locally called Thornapple. The chief chemical constituents are found such as Hyoscyamine and hyoscine and meteloidine were found in the leaves, flowers, pericarp and seeds of the plant root gave tropane, tropine and pseudotropine. Some other chemical constituents have been found as tropane alkaloids, hyoscyamine and hyoscine are clinically more significant. It is used in pre-anaesthetic (Dabur et al 2004) surgery and childbirth, in ophthalmology and for the prevention of motion sickness (Khan et al., 2009) and investigated solanaceae species of *Datura stramonium* Leaf of *D. stramonium* leaf powder showed action like anaesthetic agent. They reported the *D. stramonium* could be used as anaesthesia in fish management at concentrations 1.0ppm to 3.0ppm (Adebayo et al., 2017).

***Erythroxylum coca* (Erythroxylaceae)**

It is locally called Coca, Cocaine Plant and Coca leaves contain a large number of alkaloids including cocaine, tropacocaine, cinnamoylcocaine, truxillines and benzoylecgonine (Alkaloid content varies from 0.5 to 1.5%). It has been reported local and anesthetic activity due to 1. Prevent the generation and the conduction of the nerve impulse. 2. The primary site of action is the cell membrane. Local anesthetics block transmission by diminishing or preventing the large transient enhance in the permeability of excitable membranes to. Na+ channels. (Voltage-gated Na+ channels) 3. As the anesthetic action gradually develops in a nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines, impulse conduction slows, and the safety factor for conduction decreases; these factors decrease the probability of propagation of the action potential, and nerve conduction fails. The bark and seeds also contain cocaine, Mydriatic anaesthetic and toxic (Kokate et al., 1977).

***Helleborus niger* Linn (Ranunculaceae)**

It is locally called black hellebore and christmas rose. Its chemical constituents are cardiac glycosides; helleborin, helleborein, hellebrin and others based on helleborigenin, roots and rhizomes gave hellebrin, desglucohellebrin, hellebrigenin, bufatetraenolide, beta-ecdysterone, 5beta-hydroxyecdysterone and bufadienolides. bufadienolides has been reported as surface anesthetic agent (Yoshida et al., 1976). Others reported uses in drastic purgative, abortifacient, diuretic, local anaesthetic and narcotic (Cheng et al., 2002; Charles et al., 2000).

***Jasminum officinale* Linn. var. grandiflorum (L.) Kobuski (Oleaceae)**

It is locally called Spanish Jasmine. The chemical constituents are found as benzyl acetate, benzyl benzoate, phytol, jasmone, methyl jasmonate, linalool, geranyl

linalool, eugenol, isophytyl acetate, and isophytol 2.4%. The leaves gave ascorbic acid, anthranilic acid and its glucoside, indole oxygenase, alkaloid jasminine and salicylic acid. The flowers contain pyridine and nicotinate derivatives .The uses of *Jasminum officinale* as Sedative, CNS depressant, astringent and mild anaesthetic used for coughs, hoarsenesses and other disorders of the chest (Al-Rawi et al., 1964).

***Mandragora autumnalis* Spreng (Solanaceae)**

It is locally called Mandrake/ roots from Morocco contained atropine (0.2% at flowering stage). The mandragora plant, or mandrake, was used as a sedative and to induce pain relief for surgical procedures. It has been reported in tablets and friezes since the 16th century and used for its sedative property. The Romans used the mandrake for surgery. It has been reported as general anaesthetic, narcotic, poisonous property (Lumıir et al., 2005).

***Pimenta dioica (Linn.)* Merrill. (Myrtaceae)**

It is usually called Allspice tree, Jamaica Pepper tree, Pimento tree, the oil of *Pimenta dioica* contains chiefly eugenol 65–80% carminative and stimulant anaesthetic effect when crushed berries are applied topically (Rao et al., 2012). Furthermore, it has been reported that Eugenol has analgesic effect in neuralgia; it is often used as anesthetic by dentists (Kamatou et al., 2012). The *Pimenta dioica* also called Allspice can be found in all continents with unique names in over 50 languages. Regular investigation of aromatic constituents of *Pimenta dioica* leaves and its unripe berries, Allspice, many other aromatic compounds has been found like glycosides and polyphenols that show antibacterial, hypotensive, anti-neuralgic and analgesic properties.

***Spergularia rubra* (Linn.) (Caryophylaceae)**

It is commonly called Sand-Spurry, Sandwort, Arenaria Rubra. Its whole plant gave alpha-and betaamyrin ester, myricyl alcohol, stigmasterol and its glucoside. Atincturemade, Spilanthol, Diuretic, mild Anaesthetic and used in cystitis and urethral colic (Chandra et al., 2015).

***Spilanthes calva* DC (Asteraceae)**

The chemical constituents are found 1-2 % Spilanthol , Isobutylamide, Choline, Tannins, Resin. It has been reported as local anesthetic activity due to following action like (IWhen chewed the flower heads produced a remarkable tingling sensation in the mouth, a local anesthetic and pronounced increases in saliva flow. (ii) These effects are due to spilanthol, which also has strong insecticidal and antimicirobial activities. (iii) Spilanthol shows a pronounced mouth watering effect on ingestion. The others uses as antidysenteric and in scabies and psoriasis. The Seeds of this plant used in xerostomia, throat infections and neurological affection of tongue. Root purgative and local anaesthetic and a powerful insecticide (Ley et al., 2006).

***Syzygium aromaticum* (Myrtaceae)**

It is locally called Clove. It is containing Eugenin, triterpene acids, crategolic acid and steroid glucosides, eugenol and acetyleugenol. It has been showed the local anesthetic activity due to following action (IThe blockade of Na+ channels that reduces action potentials and severs as local anesthetics. (ii) Inhibition of prostaglandin synthesis during cyclo-oxygenease and lipoxygenose pathway explaining its analgesic and anti-inflammatory properties. The reported other uses as carminative, antiinflammatory, antibacterial and anaesthetic (Ebadi et al., 2007).

***Valerian officinalis* (Valerianaceae)**

It is locally called Valerian, Garden Heliotrope, and Common Valerian. Its root containing valtrates, didrovaltrates and isovalerates, Other constituents include monoterpenes and sesquiterpenes, caffeic, gamma-aminobutyric (GABA) and chlorogenic acids, beta-sitosterol, methyl, 2-pyrrolketone, choline, tannins, gums alkaloids and resin. It has been showed mild anesthetic activity due to; (i) Inhibit action of GABA amino acid neurotransmitter in the brain (ii) It is inhibit the reuptake of GABA in the presynaptic vesicles and enhances the release of GABA. The *Valerian officinalis* uses as Tranquillizer, hypnotic for nervous tension, sleeplessness, restlessness, palpitation, tension, headache, migraine, menstrual pain, intestinal cramps, bronchial spasm and as mild anaesthetic agent (Ebadi et al., 2007).

***Zanthoxylum americanum* Mill (Rutaceae)**

It is locally called Toothache tree, Prickly Ash. The bark contains alkaloids gammafagarine, beta-fagarine, magnoflorine, laurifoline, nitidine, chelerythrine, tembetarine, candicine; coumarins include xanthyletine, xanthoxyletin and alloxanthyletin . It is used internally and externaly to treat rheumatism and toothache; also for circulatory insufficiency fevers and aneasthesia (Kirova et al., 2009).

***Zanthoxylum oxyphylum* Mill. (Rutaceae)**

It is locally known Mezenga. The chemical constituents are found such as Alkaloids, xanthoxyphyllin and corydine and a lactone 3,5-bis furan 2-one have been isolated from the roots. Stem bark gave zanoxyline and rhetsinine. Dried branches with bark gave lignans (sesamin, eudesmin and epieudesmin), fluoroquinolone alkaloid gamma-fagarine, triterpenoid lupeol,beta-sitosterol and syringaresinol. Its bark used as stimulant, stomachic, sudorific; used in colic, Administered in fevers. Fruits-used for dyspepsia, also for asthma, bronchitis, rheumatism and toothache (Brijwal et al., 2013).

Other herbal anesthetic phytochemical constituents and their role

Results of the literature investigation suggest that herbal

plants preparations and their containing phytochemicals have the potential to develop into local anesthetic, general anesthetic, antinociceptive, analgesic and sedative drugs. Still, well-controlled clinical trials with phytochemical drug candidates and their practical applications to humans are still inadequate. However, there is a possibility that preferred phytochemicals could lead to anesthetics and anesthesia-related compounds. The plants chemicals like terpenoids, alkaloids and flavonoids are predictable to become novel anesthetic agents of plant origin as they meet the mechanistic requirements to interact with receptors, channels and membranes and they have the characteristic molecular structures diverse from conventional drugs. The reported phytochemicals structures are summarized in figure 1. Among them, the voltage-gated Na+ channel-blocking activity showed by alkaloids (examples lappaconitine, bulleyaconitine A, 3-acetylaconitine, etc.) and terpenoids (examples menthol, thymol, carvacrol, linalool, etc.) could be the alternatives for local anesthetics. Zalachoras et al., reported the conduction changes of frog sciatic nerve fibers to compare the local anesthetic activity of five selected monoterpenes: such as acyclic linalool, monocyclic p-cymene, and bicyclic eucalyptol (1,8-cineol), α-pinene and fenchone. They found satisfactory results. The GABAA receptor-modulatory flavonoids (examples apigenin, kaempferol, baicalein, wogonin, chrysin, isoliquiritigenin, etc.) may be the pilot compounds for general anesthetics and sedatives. Some of them have been productively applied to experimental animals and humans. The clinical effectiveness, adverse action, pharmacokinetics and pharmacodynamics of these plants compounds remain to be elucidated together with structural modification to improve the activity or reduce the side effects.

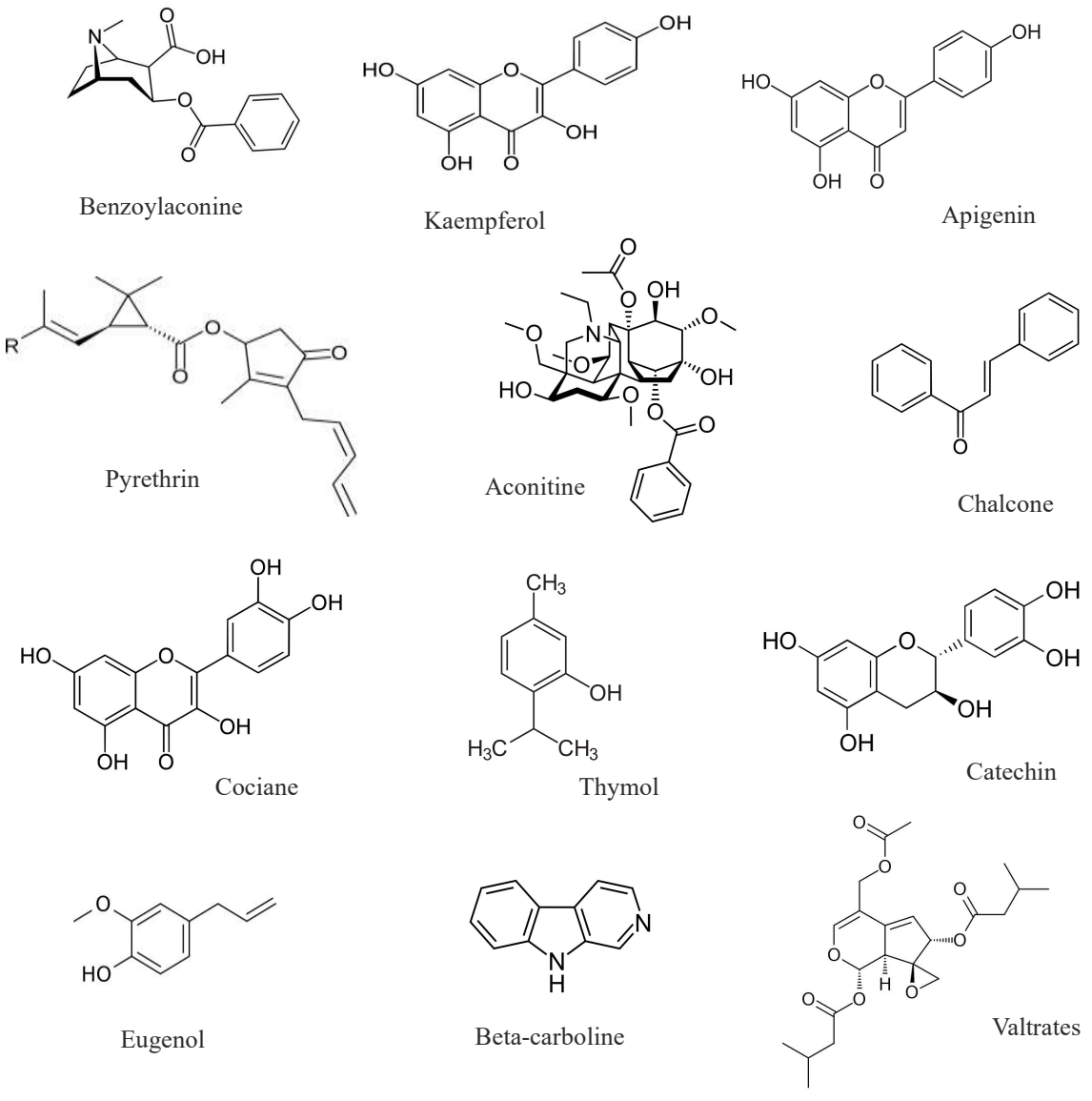

Figure 1. Structures of different chemical constituents reported as anesthetic activity (Hironori et al., 2017).

Conclusions and future prospects

It has been evident from the present review that phytochemicals serve as promising and effective research area with bright future. The growing incidence of diseases and its high cost treatments like various limitations in the conventional therapy such as high cost, and high toxicity of present drugs. Therefore severe challenge to all the researchers to design and develop an alternative, eco-friendly, biocompatible and cost-effective strategy in a greener way. Under this scenario, phyto-molecules are expected to revolutionize treatment in the next decade. High biodegradability and biocompatibility have increased the efficacy of these phytomolecules in anesthetic therapy. This comprehensive review paper provides information on medicinal plants and their role with potential to cure different types of diseases. Potential herbal plants described in this comprehensive review article should be further researched in clinical trials (Coca, Clove, Cinchona, Dhatura, Jasmine, Eugenol, Spilanthes etc.) on different models for their effectiveness and toxicological documentation. Furthermore, extensive research work should be carried out on these phytochemicals to evaluate their possible applications, toxicological and particular genotoxic profile against a wide range of cancer in both either *in-vitro or in-vivo*.

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