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REVIEW ARTICLE

Phytochemistry and Polypharmacological Potential of *Colebrookea Oppositifolia* Smith

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Abstract: ***Background*:** *Colebrookea oppositifolia* Smith. is a valuable traditional therapeutic plant belonging to the family Lamiaceae. It is a dense and wool-like shrub that is mostly found in subtropical regions of some countries of Asia, such as China and India. It has been widely used for the mitigation of nervous system disorders like epilepsy. The active constituents of the plant have exhibited antioxidant, anti-microbial, and antifungal properties, which are considered due to the presence of polyphenols and flavonoids as chief chemical constituents. Flavonoids like quercetin, landenein, chrysin, and 5, 6, 7-trimethoxy flavones cause protein denaturation of the microbial cell wall.

***Objectives*:** To comprehend and assemble the fragmented pieces of evidence presented on the traditional uses, botany, phytochemistry, and pharmacology of the plant to reconnoiter its therapeutic perspective and forthcoming research opportunities.

***Methods*:** The available information on *Colebrookea oppositifolia* has been established by electronically searching peer-reviewed literature from PubMed, Google Scholar, Springer, Scopus, Web of Science, and Science Direct over the earlier few years.

***Results*:** The plant has been greatly used for the preparation of many herbal medicines which are used for treating traumatic injuries, fever, rheumatoid arthritis, headache, and gastric problems. From the aerial parts of the plant, a phenylethanoid glycoside named acteoside has been isolated and evaluated for its therapeutic potential *viz*. immunomodulatory, neuroprotective, hepatoprotective, analgesic, anti-tumour, antispasmodic, antioxidant, antibacterial, free radical scavenger, and improving sexual function. Acteoside showed neuroprotective activities against Aβ-peptide, which is neurotoxic and causes apoptosis. The petroleum ether extract of the plant leaves offers many active compounds like sitosterol, n-triacontane, hydroxydotriacontyl ferulate, acetyl alcohol, and 3,7,4,2-tetramethoxyflavones which have shown hepatoprotective potential.

***Conclusion*:** The plant should be evaluated further for the estimation of some other health benefits. The consequences of restricted pharmacological screening and reported phytomolecules of *Colebrookea oppositifolia* Smith. advocate that there is still an exigent requisite for in-depth pharmacological studies of the plant.

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1. INTRODUCTION

Colebrookea is a genus that belongs to the Lamiaceae family of plants. It consists of the well-known species *Colebrookea oppositifolia* Smith. [1]. It is an intense woolly shrub generally distributed in Indian hilly parts [2, 3]. In the traditional system of medicine, plant leaves are mainly utilized for healing bruises and wounds, and roots are applied for treating epilepsy [4]. Several polyphenols and flavonoids present in the plant are accountable for antioxidant, antimicrobial, and antifungal properties. It is also applied for treating corneal opacity, conjunctivitis, and sore eyes due to its anti-inflammatory actions [5, 6]. Colebrookea has anthelmintic activities used in pinworms, roundworms, and tapeworm infections and is also utilized in the amelioration of dysentery, nose bleeds, dermatitis, and bloody coughs [7]. The plant constituents are generally employed to cure the ailments such as fever, urinary problems, epilepsy, and headache. It possesses cardioprotective, anti-inflammatory, and hepato-protective attributes [8, 9].

Colebrookea oppositifolia has been used in treating various diseases. The present article focused on active chemical constituents and therapeutic actions of Colebrookea in different fields. The Introduction section includes the background and aims of the research comprehensively for the researchers.

1.1. Description

The plant height is about 1-3 m. Branches are hairy and mostly pale in color, and stems are solid and light-colored. The leaves are light in green, usually whitish hairy from the bottom and darkish green at the top [10]. Occasionally, the leaves are arranged in spirals of 3. The leaves are generally fine, elongated and 10-15 cm long [11]. Several thin white flowers arise in the form of upright spikes, about 5-10 cm long. Colebrookea is also known as Indian squirrel tail due to the presence of spikes bearing flowers that appear hairy similar to a squirrel's tail. The flowering period of the plant is from December to April [12].

1.2. Distribution

Colebrookea oppositifolia is a subtropical plant. It is universally distributed and belongs to dicotyledonous, seed-forming plants, containing more than 240 genera and 6500 species. It is cultivated in the subtropical Himalayas, Indian hills, and plains regions such as Madhya Pradesh, Bihar, Sikkim, and central India. It is also cultivated in China, Burma, Thailand, Nepal, Myanmar, and Bhutan [4, 13-15].

1.3. Pharmacological Significance

Natural products are the supreme fortune of nature. Several plant-based molecules are in clinical use and in the clinical development phase [16-20]. Numerous phytomolecules have been obtained from plants like alkaloids, tannins, glycosides, coumarins, lignans, flavonoids, and polyphenolic constituents, *etc*. are documented in the literature, which have been screened for an array of biological activities [21-27]. Natural products are widely used with high biocompatibility, low toxicity, good sustainability, and respectable safety profiles.

Colebrookea oppositifolia has enormous medicinal potential and is customarily pragmatic to cure hepatitis, epilepsy, and UTI disorders [28-30]. It is also employed as an antimicrobial agent [31-33]. Leaves of the plant are given to cattle to curb anthrax infection. The warmed leaves were applied to the strains [34]. Leaf paste is applied on tongue sores, toothache, fractured bone, wounds, and also in the mouth [35-37]. It considerably enhances the mucus of the gastrointestinal tract and extensively leads to the reduction in peptic ulcers in rat models. The antioxidant and mucoprotective potential of the hydro-alcoholic extract from the roots of *Colebrookea oppositifolia* are responsible for its antiulcer activity [38]. Apart from these, *Colebrookea oppositifolia* is also used as an anthelmintic against ringworms [39]. Young twigs are usually utilized as a toothbrush. The juice of the young plant is poured into nostrils for treating sinusitis and also administered to relieve GIT disorders. Plant roots are significantly used for their anti-fertility activity [40-42]. Methanol, water and chloroform extracts from the leaves of *Colebrookea oppositifolia* have been investigated for their *in vitro* antibacterial activity against *Escherichia coli*, *Micrococcus luteus*, *Trobacter freumdii*, and *Neisseria mucosa*. The aqueous extract of leaves has shown less zone of inhibition in comparison to the standard [43]. The pharmacological actions of Colebrookea have been depicted in Fig. (**1**).

2. PHYTOCHEMISTRY

Colebrookea oppositifolia consists of many flavonoids and polyphenolic compounds. The petroleum ether extract from the leaves of the plant affords five important constituents named *β*-sitosterol (**1**), 32-hydroxydotriacontyl ferulate (**2**), n-triacontane (**3**), 5,6,7,4′-tetramethoxyflavone (**4**), and cetyl alcohol (**5**) [44-49]. Some of the other medicinal compounds isolated root of *Colebrookea oppositifolia* includes palmitic acid (**6**), triacontanol (**7**), stearic acid (**8**), oleic acid (**9**), flavone glycosides; 5,6,7-trimethoxyflavone (**10**), echioidin (**11**) and 4',5,6,7-tetramethoxyflavone were extracted from the methanolic extract [2, 50]. The bark contains quercetin (**12**), 5,6,7-trimethoxyflavone, and stigmasterol (**13**) [51, 52]. Flavone glycosides such as negletein (**14**), landenein (**15**), and chrysin (**16**) were isolated from the methanolic extract of the bark from the plant [53-56].

The essential aromatic compounds isolated from *Colebrookea oppositifolia* are recognized as 9,12,15- octadecatrienoic acid, *n*-hexadecanoic acid, phytol, and octanoic acid, succinic anhydride [57]. 9,12,15-Octadecatrienoic acid, which is also known as *α*-Linolenic acid is identified as an essential fatty acid [58]. *n*- Hexadecanoic acid, also known as palmitic acid is utilized to manufacture cosmetics, soaps, and lubricating agents [59]. Octanoic acid tridec-2-enyl ester also known as caprylic acid and is used mainly for the manufacturing of dyes and also in the production of perfumes. The structure of phytomolecules of *Colebrookea oppositifolia* was presented in Figs. (**2** and **3**). [60]. Hydrogenation of palmitic acid produces acetyl alcohol that is used to form detergents [61]. Luteolin-7-glucoside (**17**) and eugenol (**18**)

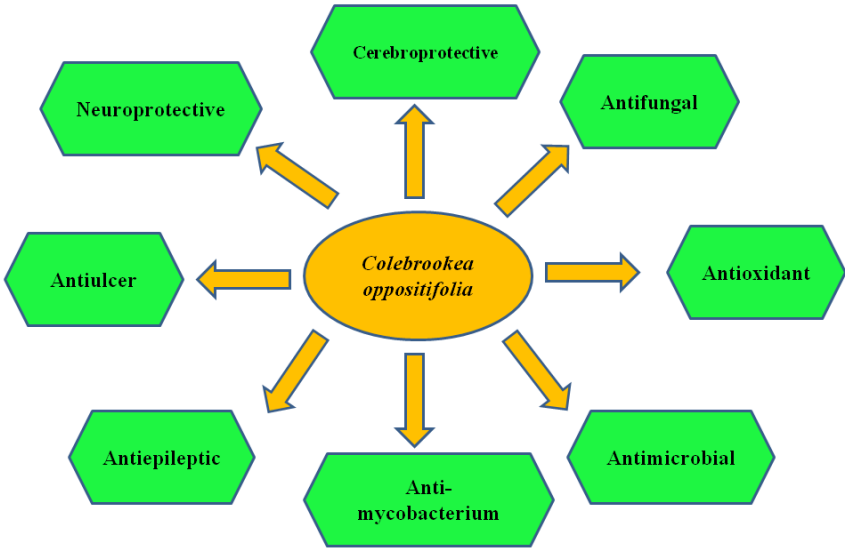


Fig. (1). Pharmacological actions of *Colebrookea oppositifolia.* (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

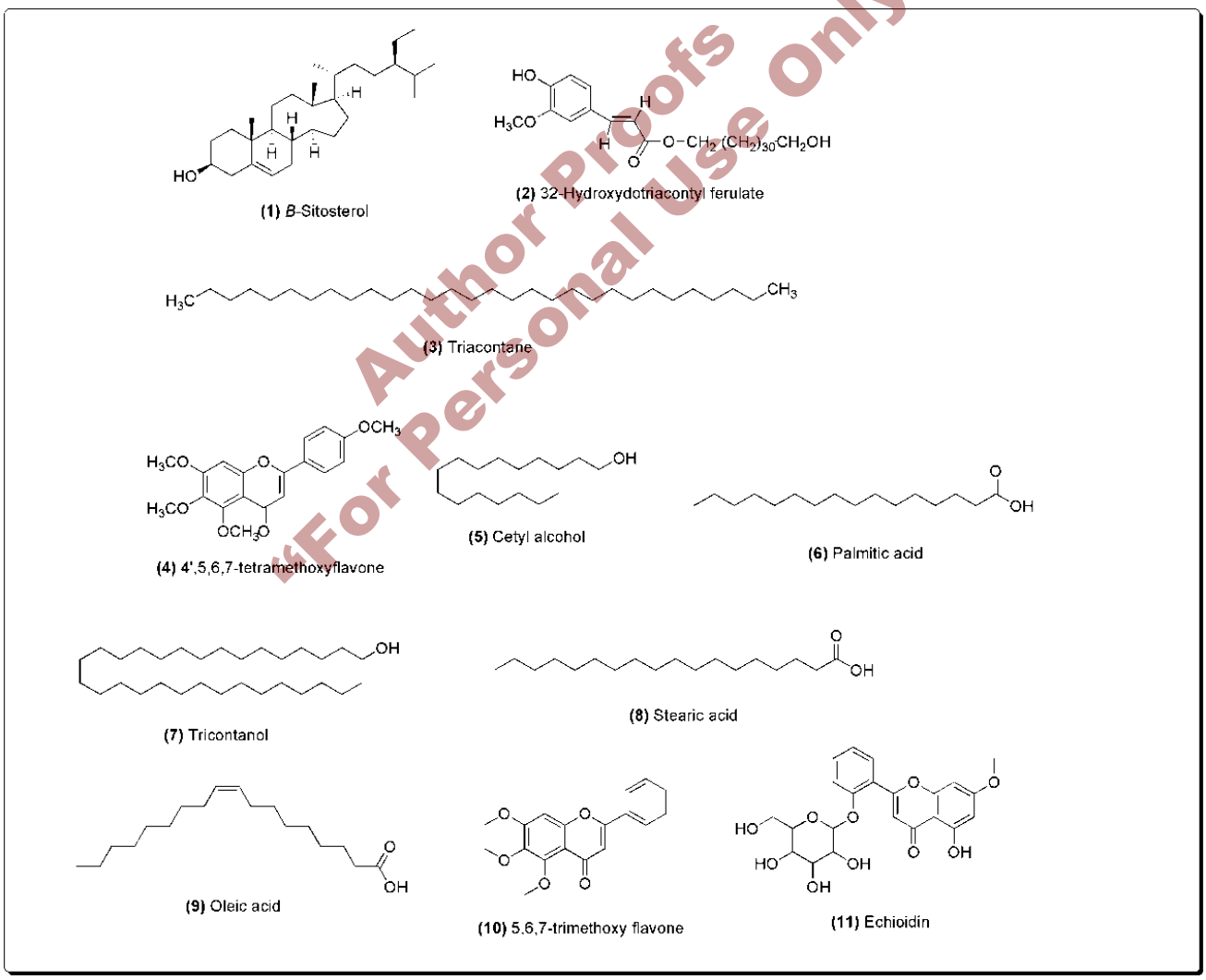


Fig. (2). Structures of compounds (**1-11**). Compounds (**1-9**) were isolated from petroleum extract obtained from the leaves of the *Colebrookea oppositifolia* plant and (**10** and **11**) from methanol extract obtained from the root part of this plant.

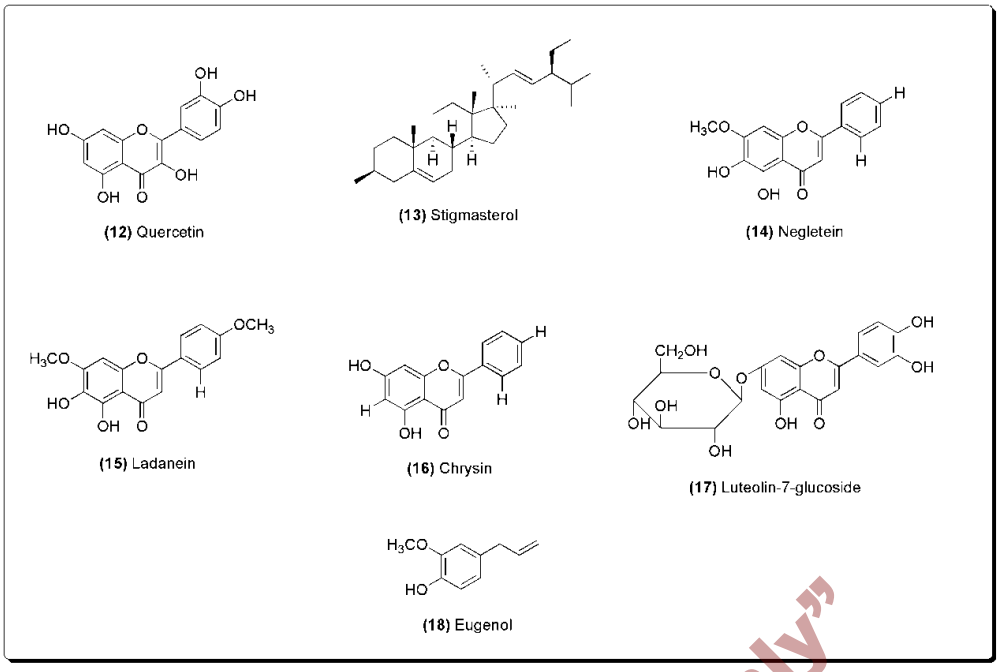


Fig. (3). Structures of compounds (**12-18**). Compounds (**12-16**) were isolated from the methanol extract of bark whereas compounds **17** and **18** were from the methanol extract of leaves of *Colebrookea oppositifolia*.

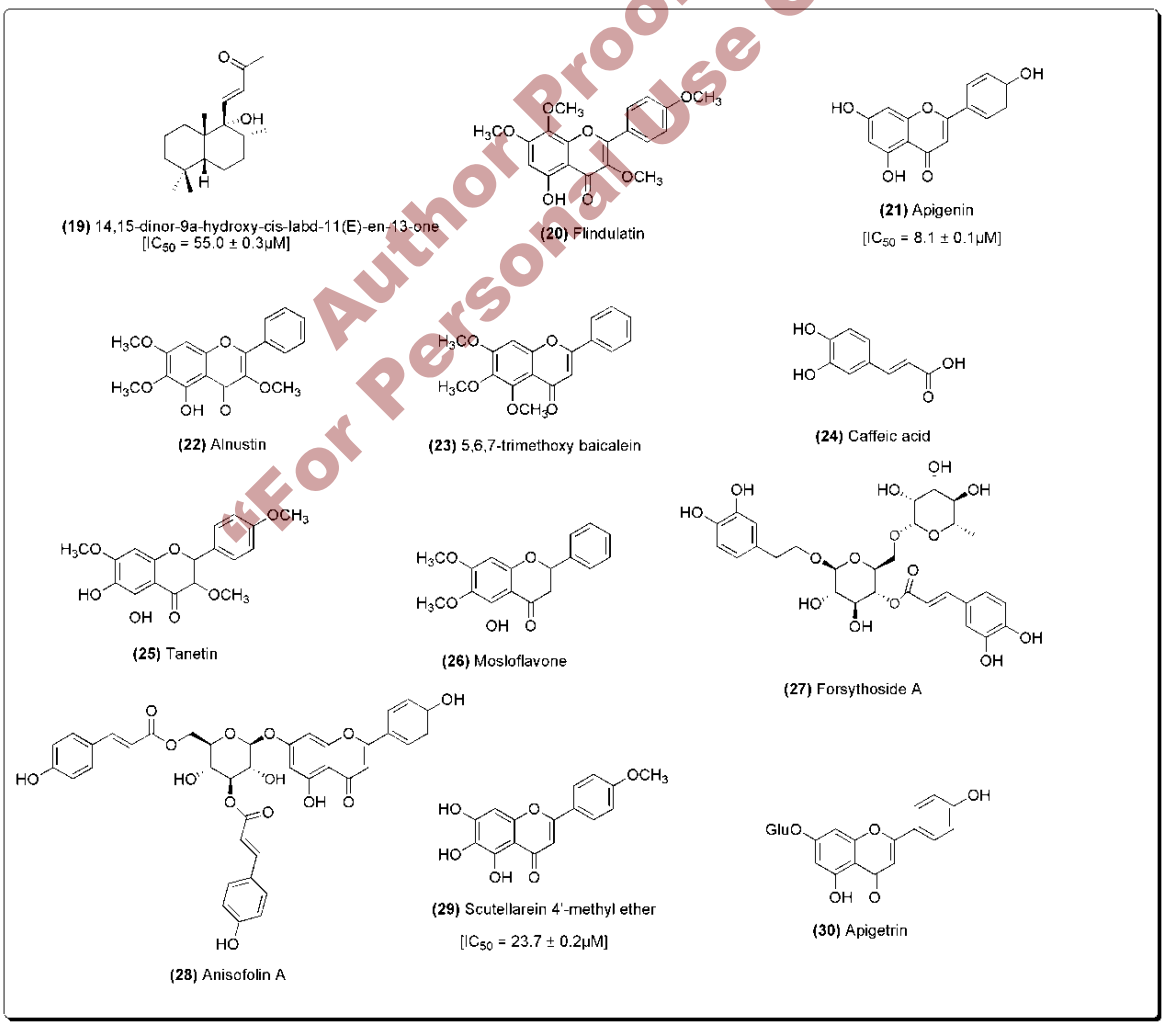
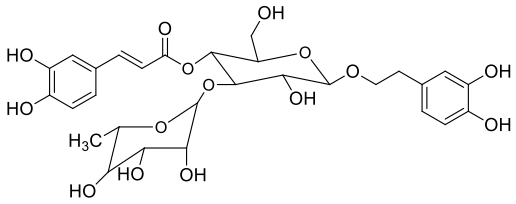


Fig. (4). Structures of compounds (**19-30**). Acetone extract from the aerial part of the plant gives compounds (**19-30**).



(31) Acteoside

Fig. (5). Structure of acteoside. Acteoside isolated from aqueous ethanol extract of aerial part of *Colebrookea oppositifolia*.

have been isolated from methanolic extract of leaves of the plant and screened for their antimicrobial potential [62-64].

Similarly, acetone extract prepared from aerial parts of Colebrookea, a novel labdane diterpene known as 14,15-dinor-9α-hydroxy-cis-labd-11(*E*)-en-13-one (**19**) is extracted [65]. Some other compounds that were isolated from this plant include flindulatin (**20**) [66], apigenin (**21**) [67], alnustin (**22**) [68], 5,6,7-trimethoxy baicalein (**23**) [69], caffeic acid (**24**) [70], tanetin (**25**) [71], mosloflavone (**26**) [72], forsythoside A (**27**) [73], anisofolin A (**28**) [74], scutellarein 4′-methyl ether (**29**) [75], and apigetrin (**30**) [76]. Structures of compounds (**19**-**30**) were presented in Fig. (**4**).

A potential therapeutic candidate named acteoside (**31**) depicted in Fig. (**5**), is isolated from the aerial parts of *Colebrookea oppositifolia* and has shown significant antifungal activity in conjunction with amphotericin B (AmB). Acteoside is significantly distributed in the plant kingdom have been isolated using extraction with aqueous ethanol. Ali *et al.* reported the extraction of aerial parts of the plant (500 g) yields 90 g of extract from which 18% of acteoside has been isolated using column chromatography [77].

3. THERAPEUTIC POTENTIAL OF *COLEBROOKEA OPPOSITIFOLIA* (ETHNOPHARMACOLOGY)

From the extensive literature review, it has been established that *Colebrookea oppositifolia* exhibits an ample range of therapeutic properties for the treatment of diverse disorders. Some of its potential therapeutic activities are described below.

3.1. Anti-epileptic Activity

Epilepsy is a severe disorder of the central nervous system affecting more than 65 million people around the world, and about 0.2 million populations are freshly diagnosed with epilepsy every year [78, 79]. It is approximated that about 1 million deaths take place due to epilepsy every year [80, 81]. Presently, several synthetic anti-epileptic drugs are available for the management of epilepsy [82]. But, all the currently available synthetic antiepileptic drugs are more prone to produce various adverse effects such as mental confusion, dizziness, impaired concentration, sleep disturbance, aggression, mental slowing, and anorexia [83-85]. Hence, herbal medicines have become a point of focus for many researchers to invent safe and better drugs for epilepsy [86]. In this assemblage, *Colebrookea oppositifolia* has been broadly used in the therapy of several disorders and the roots of the plant *Colebrookea oppositifolia* had been extensively used for the mitigation of epilepsy. Kritikar *et al.* reported the antiepileptic action of methanolic extract of *Colebrookea oppositifolia* using experimental models of epilepsy such as Pentylenetetrazole (PTZ)- induced tonic and clonic convulsions and estimation of GABA levels in brain. The results reveals that the methanolic extract showed the significant increase in brain GABA levels in a single and multiple doses of 100 mg/kg and 300 mg/kg, respectively. Similarly, methanolic extract of *Colebrookea oppositifolia* also prolonged the onset of tonus and clonus in a dose of 25, 50 and 100 mg/kg in PTZ induced seizure. Moreover, the extract in high dose of 200 mg/kg completely inhibited the seizure induced by PTZ [87-90]. The ED_{50} value of methanolic extract of *Colebrookea oppositifolia* was found to be 26.66 mg/kg. The outcomes advocate that the methanolic extract of *Colebrookea oppositifolia* holds momentous antiepileptic actions. Furthermore, the results inveterate the engrossment of GABAergic mechanisms accountable for antiepileptic effects of methanolic extract of *Colebrookea oppositifolia* roots.

3.2. Anti-mycobacterium Activity

Tuberculosis (TB) is an infectious disease of the respiratory system caused by a mycobacterium that occurs worldwide. Approximately 8 million populations are infected with *Mycobacterium tuberculosis* every year and around 2-3 million deaths occur due to this contagious disease [91-96]. *Colebrookea oppositifolia* is used extensively for its anti-mycobacterial potential against various mycobacterium species [91, 97].

All the compounds (**19**-**30**) presented in Fig. (**4**) were evaluated against the *Mycobacterium bovis* and *Mycobacterium tuberculosis*; H37Ra for their anti-mycobacterium activity. The IC_{50} value of compound (**19**) against *M. tuberculosis* H37Ra is given as 55.0 ± 0.3 µM in the active phase. The IC_{50} values of compounds (**21**) and (**29**) against *M. tuberculosis* H37Ra are given as 8.1 ± 0.1 µM and 23.7 ± 0.2 µM respectively in the active phase [98-101].

3.3. Antibacterial Activity

Infectious and microbial diseases are caused by a variety of microorganisms and are the chief troubles of today's world. Approximately 57 million populations die every year around the world due to these diseases [102-105]. It has been demonstrated that natural plants can be a prosperous source of resilient antimicrobial agents [106-110]. The flavonoids obtained from the whole plant extracts of *C. oppositifolia* are investigated to be fungicidal and bactericidal [111, 112].

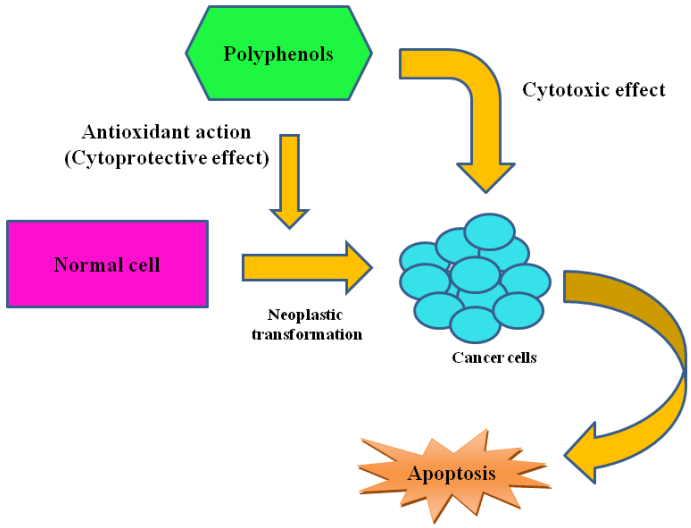


Fig. (6). Antioxidant action of polyphenolic compounds in cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Soman *et al.* has been reported that the strains of *Bacillus, Staphylococcus aureus*, and *Vibrio cholerae* are extremely sensitive to the extract of *C. oppositifolia*. However, *Shigella, E. coli*, and *Salmonella* are moderately sensitive and the strains of *Pseudomonas* and *Klebsiella* are fairly resistant to the plant extract [113-117].

3.4. Antifungal Activity

Acteoside has been isolated from the aerial parts of the plant. It has been reported to exhibit multifarious pharmacological actions like antioxidant, anti-proliferative, hepatoprotective [118], antitumor, anti-inflammatory, immunomodulatory, antispasmodic, neuroprotective, free radical scavenger potential, improving sexual functions, analgesic, sedative and vaso-relaxant [119-121]. Furthermore, a combination of inhibitory concentrations of acteoside with amphotericin B expressed strong fungicidal activity. This synergistic fungicidal action is reported to be more effective for *Cryptococcus neoformans* in comparison to *Aspergillus fumigatus* and *Candida albicans* [122-126].

3.5. Antioxidant Activity

Natural herbs containing flavonoids and polyphenolic compounds are reported to exhibit antioxidant activities [127, 128]. Acteoside, which is isolated from *Colebrookea oppositifolia* is investigated to be a potent antioxidant [119, 129]. It has been reported that amphotericin B is protected from auto-oxidation by antioxidants; hence they reduce the rate of spontaneous inactivation and extend its biological potential [130, 131].

The catechol group of acteoside is also considered to inhibit lipid peroxidation and scavenge free radicals [132, 133]. It is investigated that the antioxidant properties of catecholic compounds [134, 135] are somewhat because they protect against glutathione depletion. Polyphenols prevent apoptosis induced by reactive oxygen species (ROS) and show their cytoprotective effect (Fig. **6**) [136, 137].

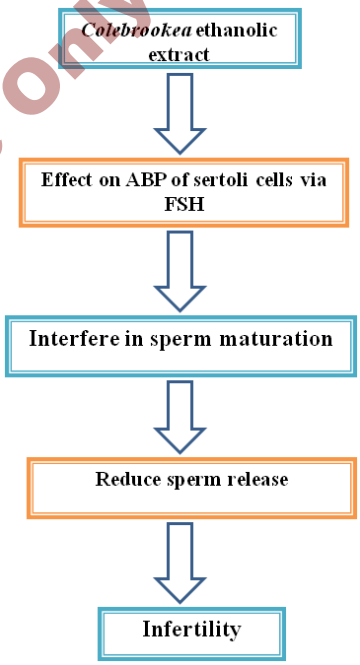


Fig. (7). A flow chart representing infertility activity.

3.6. Infertility Activity

Gupta *et al.* established infertility action in 2001, in which ethanol extract of leaves of *Colebrookea oppositifolia* is administered orally to male rats at 100 and 200 mg/kg dosage for 8-10 weeks. This dosing does not cause any reduction in their body weights, but it causes a notable decrease in the weights of reproduction parts of rats such as epididymis and testis. Treated rats have shown a significant decrease in spermatogenesis [138]. Administration of *C. oppositifolia* leaf extract orally for about 60 days in male rats brings about a significant reduction in the weight of the testis, which is considered to be due to the presence of a variant number of spermatozoa and spermatids in the tissue. The

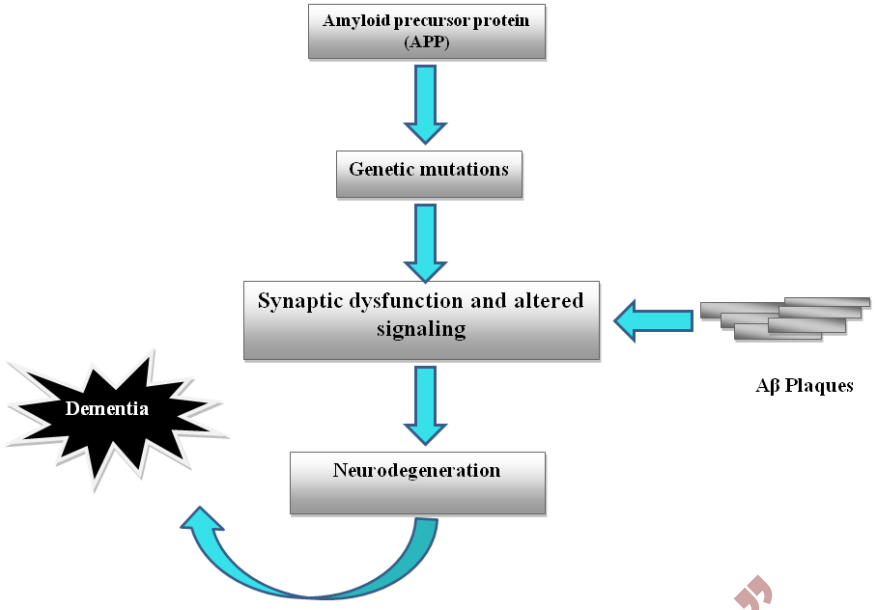


Fig. (8). Representation of possible events involved in neurodegeneration and dementia. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

infertility action of *Colebrookea oppositifolia* was presented in Fig. (**7**) [139-143].

3.7. Cerebroprotective Activity

Ischemic stroke is one of the most common and severe neuropathological conditions of vascular origin. It is caused due to the blockage of brain arteries which results in the severe reduction of blood flow toward the brain [144-147]. It has been estimated that around 6.5 million or more deaths occur annually due to ischemic stroke and it has been considered the second major leading cause of death. This is also the foremost reason for long-termed severe and serious disability [148-150].

Various drugs have been recommended for the treatment of ischemic strokes, such as compounds belonging to the pharmacological class of anti-inflammatory, calcium channel blockers, antioxidants, excitatory neurotransmitter (glutamate) receptor blockers, and anti-apoptotic agents are considered to be helpful in the management of cerebral stroke [151, 152]. Several plant-based natural drugs [153-157], herbomineral formulations [158-165], and calcium channel blockers such as nilvadipine [166], verapamil [167], and nicardipine [166] are well-approved drugs for protecting against the ischemia-induced cerebral injury in experimental animals.

Colebrookea oppositifolia is extensively used for its antioxidant and anti-inflammatory properties [168, 169]. Considering these properties of Colebrookea, it is further evaluated by Viswanatha *et al.* in 2018 for its cerebroprotective potential against ischemic stroke-induced brain injury [170-182].

3.8. Neuroprotective Activity

Neurodegeneration is generally characterized by functional and complete loss of nerve cells, neurons, and nerves which results in neuronal death. Various neurological disorders are associated with neurodegeneration, such as Parkinson's disease, multiple sclerosis, and Alzheimer,s disease (AD). In addition, other factors also contribute to neurodegenerative diseases like lifestyle, mental accumulation, nutritional habits, and environmental factors [182, 183-185]. Alzheimer's is a chronic neurodegenerative disease that influences less than 1% of people below the age of 60 and around more than 40% of populations above the age of 85 [186-188].

Alzheimer's is characterized by the deposition of intracellular neurofibrillary tangles like intracellular hyper-phosphorylated tau proteins and the deposition of β-amyloid (Aβ) plaques in the brain, which causes loss of neurons. Microglial activation results in the enhancement of acetylcholinesterase (AChE) levels and also promotes the production of free radicals. Some genetic factors, including amyloid precursor protein mutations are also involved in the progress of AD presented in Fig. (**8**) [186, 189-193].

Acteoside (**31**), which is an important chemical constituent of *Colebrookea oppositifolia*, is extensively used for its neuroprotective properties [194]. The β-amyloid peptide is usually neurotoxic *via* stress-dependent, oxidative and apoptotic processes in neuronal cells of the brain. Oxygen-free radicals are responsible for mediating the Aβ-peptide neurotoxicity and it is attenuated by free radical scavengers and antioxidants. Acteoside, which is widely accepted for its antioxidant property and thus, is reported to prohibit Aβ-induced neurotoxicity. Acteoside prevents neuronal cell death mediated by MPP+ (1-methyl-4-phenylpyridinium ion) and glutamate. In addition, acteoside exhibits significant neuroprotective activity toward the cell injury induced by Aβ-peptide. It also prevents Aβ-induced DNA damage depicted in Fig. (**9**) [195, 196].

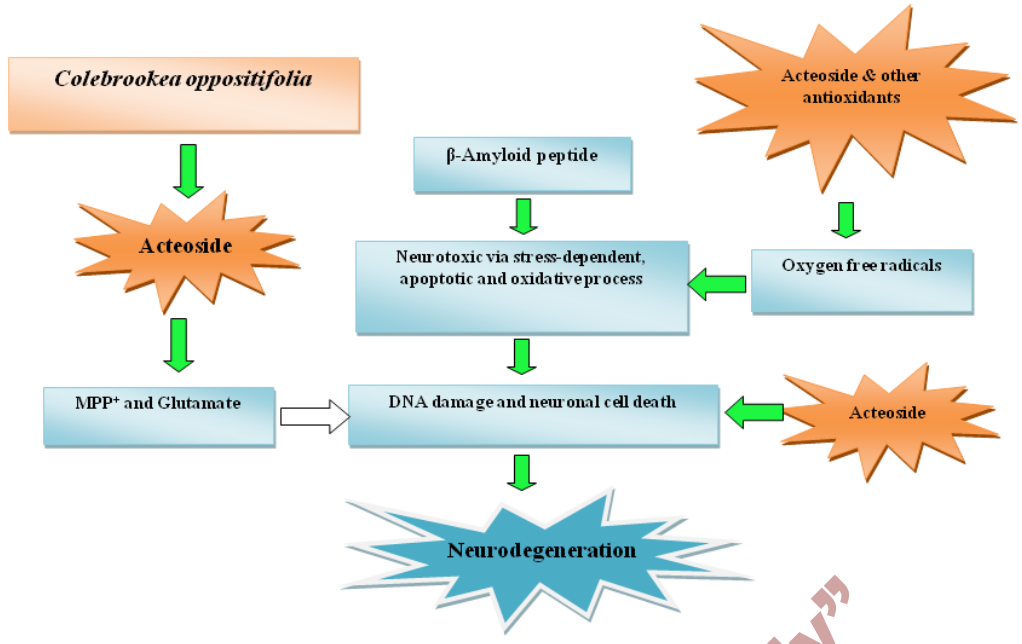


Fig. (9). Representation of the neurodegeneration process along with the neuroprotective activity of acteoside. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.9. Anti-ulcer Activity

A peptic ulcer is the most prevalent disorder of the gastrointestinal system and is considered to have a supreme clinical impact [197-199]. It is generally occupied due to an imbalance between offensive factors such as acid-pepsin secretion, bile, *Helicobacter pylori*, decreased antioxidants, and increased free radicals *versus* protective mucosal barriers, such as mucus, prostaglandins, bicarbonate secretion, the process of regeneration from cellular or tissue injury, and blood flow [200-202]. Gastric mucosal protection is carried out by using several mechanisms which include bicarbonate production, an increase in the gastric mucosal defense system, reducing the quantity of gastric acid secretion, and neutralization of gastric acid [203].

In the traditional medicinal system, several herbal and natural drugs are used to treat peptic ulcers [204-209]. *Colebrookea oppositifolia* is used to treat various diseases. Dash *et al.* reported that the root extract of *Colebrookea oppositifolia* is used to treat peptic ulcers [210-215].

CONCLUSION

This review article presents the structures of the most phytomolecules isolated from various extracts prepared from leaves, barks, roots, and aerial parts of the plant and screened by eminent researchers, scientists, and scholars globally for numerous biological activities. The literature survey indicates the promising attributes of several new phytomolecules discovered and have therapeutic potential in the mitigation of a wide variety of diseases. The assemblage highlights an overview of talented phytomolecules, their structures, description, and distribution of plants along with ethnopharmacological relevance documented in numerous research reports.

Several studies established by the scientific community on *Colebrookea oppositifolia* concluded that the plant has numerous therapeutic properties and health benefits. A variety of chemical constituents found in the plant play an extensive role in the amelioration of different diseases. The methanolic root extract of *Colebrookea oppositifolia* enhances the levels of GABA-nergic inhibitory neurotransmitters in the brain and thus exhibits anticonvulsant activity. From the acetone extract of the aerial parts of *Colebrookea*, a novel labdane diterpene known as 14,15-dinor-9α-hydroxy-cis-labd-11(E)-en-13-one is isolated and employed in the management of tuberculosis. Several polyphenols and flavonoids obtained from the plant have shown potent antioxidant and free radical scavenging properties. The steroidal constituents help improve sexual functions. Administration of *C. oppositifolia* leaf extract orally for about 60 days in male rats causes infertility. Treatment of animals with methanolic extract of *C. oppositifolia* has expressed major protection against ischemia-reperfusion-induced neurological death. Acteoside, which is an important chemical constituent of *Colebrookea oppositifolia*, is extensively used for its neuroprotective activities. Treatment with root extract of *Colebrookea oppositifolia* has greatly increased the glutathione levels in the gastric tissues and thus exhibited antiulcer activity. At a glance, *Colebrookea oppositifolia* is a God gifted for the amelioration of several ailments.

LIST OF ABBREVIATIONS

µM	=	Micro molar
AChE	=	Acetylcholinesterase
AD	=	Alzheimer disease
AmB	=	Amphotericin B

DNA = Deoxyribonucleic acid

GABA = Gamma-aminobutyric acid

GIT = Gastrointestinal tract

IC_{50} = Inhibit cellular proliferation by 50 %

MECO = Methanolic extract of *Colebrookea oppositifolia*

MPP = 1-methyl-4-phenylpyridinium ion

ROS = Reactive oxygen species

UTI = Urinary tract infections

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Ishtiaq, S.; Meo, M.B.; Afridi, M.S.K.; Akbar, S.; Rasool, S. Pharmacognostic studies of aerial parts of Colebrookea oppositifolia Sm. *Ann. Phytomed.*, **2016**, *5*(2), 161-167. http://dx.doi.org/10.21276/ap.2016.5.2.23

[2] Reddy, R.V.N.; Reddy, B.A.K.; Gunasekar, D. A new acylated flavone glycoside from *Colebrookea oppositifolia*. *J. Asian Nat. Prod. Res.*, **2009**, *11*(2), 183-186. http://dx.doi.org/10.1080/10286020802674871 PMID: 19219733

[3] The Wealth of India. A dictionary of Indian raw materials and industrial products. In: *CSIR, New Delhi*; **1956**; II, p. 308.

[4] Chopra, R.N.; Nayar, S.L.; Chopra, I.C. *Glossary of Indian Medicinal Plants*; CSIR Publication: New Delhi, **1956**, pp. 74.

[5] Torri, M.C. Mainstreaming local health through herbal gardens in India: a tool to enhance women active agency and primary health care? *Environ. Dev. Sustain.*, **2012**, *14*(3), 389-406. http://dx.doi.org/10.1007/s10668-011-9331-7

[6] Joseph, S.V.; Edirisinghe, I.; Burton-Freeman, B.M. Fruit polyphenols: A review of anti-inflammatory effects in humans. *Crit. Rev. Food Sci. Nutr.*, **2016**, *56*(3), 419-444. http://dx.doi.org/10.1080/10408398.2013.767221 PMID: 25616409

[7] Venkateshappa, S.M.; Sreenath, K.P. Potential medicinal plants of Lamiaceae. *Am. Int. J. Formal. Res. App. Nat. Sci.*, **2013**, *3*, 82-88.

[8] Holley, J.; Cherla, K. *Medicinal plants sector in India. A review of medicinal and aromatic plants program in Asia (MAPA)*; SARO/IDRC: New Delhi, India, **1998**, p. 109.

[9] Robak, J.; Gryglewski, R.J. Bioactivity of flavonoids. *Pol. J. Pharmacol.*, **1996**, *48*(6), 555-564. PMID: 9112694

[10] Madhavan, V.; Yadav, D.K.; Gurudeva, M.; Yoganarasimhan, S. Pharmacognostical studies on the leaves of *Colebrookea oppositifolia* Smith. *J. Trad. Med.*, **2011**, *6*, 134-144.

[11] Santapu, H.; Henry, A. *A Dictionary of the Flowering Plants of India*; CSIR: New Delhi, **1976**, pp. 42.

[12] Cantino, P.D. Evidence for a polyphyletic origin of Labiatae. *Ann. Mo. Bot. Gard.*, **1992**, *79*(2), 361-379. http://dx.doi.org/10.2307/2399774

[13] Tanaka, N.; Koyama, T.; Murata, J. The flowering plants of Mt. Popa, central Myanmar - Results of Myanmar-Japanese joint expeditions. *Makinoa*, **2005**, *5*, 1-102.

[14] Rahman, M.O. Second list of angiospermic taxa of Bangladesh not included in Hooker's 'Flora of British India' and Prain's 'Bengal Plants': series I. *Bangladesh J. Plant Taxon.*, **2004**, *11*, 77-82.

[15] Khanam, M.; Hassan, M.A. Lamiaceae. *Flora of Bangladesh.*, **2008**, *58*, 1-161.

[16] Kumar, D.; Sharma, P.; Singh, H.; Nepali, K.; Gupta, G.K.; Jain, S.K.; Ntie-Kang, F. The value of pyrans as anticancer scaffolds in medicinal chemistry. *RSC Advances*, **2017**, *7*(59), 36977-36999. http://dx.doi.org/10.1039/C7RA05441F

[17] Kumar, D.; Kumar Jain, S. A Comprehensive review of N-heterocycles as cytotoxic agents. *Curr. Med. Chem.*, **2016**, *23*(38), 4338-4394. http://dx.doi.org/10.2174/0929867323666160809093930 PMID: 27516198

[18] Sharma, P.; Sharma, R.; Rao, H.S.; Kumar, D. Phytochemistry and medicinal attributes of *A. scholaris*: A review. *Int. J. Pharm. Sci. Res.*, **2016**, *7*(2), 1000-1010. http://dx.doi.org/10.13040/IJPSR.0975-8232.6(12).505-13

[19] Kaur, T.; Sharma, P.; Gupta, G.; Ntie-Kang, F.; Kumar, D. Treatment of tuberculosis by natural drugs: A review. *Plant Arch.*, **2019**, *19*(2), 2168-2176.

[20] Kumar, D.; Sharma, P.; Shabu, ; Kaur, R.; Lobe, M.M.M.; Gupta, G.K.; Ntie-Kang, F. In search of therapeutic candidates for HIV/AIDS: rational approaches, design strategies, structure–activity relationship and mechanistic insights. *RSC Advances*, **2021**, *11*(29), 17936-17964. http://dx.doi.org/10.1039/D0RA10655K PMID: 35480193

[21] Kaur, R.; Sharma, P.; Gupta, G.K.; Ntie-Kang, F.; Kumar, D. Structure-activity-relationship and mechanistic insights for anti-HIV natural products. *Molecules*, **2020**, *25*(9), 2070. http://dx.doi.org/10.3390/molecules25092070 PMID: 32365518

[22] Sharma, P.; Shri, R.; Ntie-Kang, F.; Kumar, S. Phytochemical and ethnopharmacological perspectives of *Ehretia laevis. Molecules*, **2021**, *26*(12), 3489. http://dx.doi.org/10.3390/molecules26123489 PMID: 34201193

[23] Kumar, D.; Malik, F.; Bedi, P.M.S.; Jain, S. 2,4-diarylpyrano[3,2-c]-chromen-5(4H)-ones as coumarin-chalcone conjugates: Design, synthesis and biological evaluation as apoptosis inducing agents. *Chem. Pharm. Bull. (Tokyo)*, **2016**, *64*, 399-409. http://dx.doi.org/10.1248/cpb.c15-00958 PMID: 27150472

[24] Kumar, D.; Singh, G.; Sharma, P.; Qayum, A.; Mahajan, G.; Mintoo, M.J.; Singh, S.K.; Mondhe, D.M.; Bedi, P.M.S.; Jain, S.K.; Gupta, G.K. 4-aryl/heteroaryl-4*H*-fused pyrans as anti-proliferative agents: Design, synthesis and biological evaluation. *Anticancer. Agents Med. Chem.*, **2018**, *18*(1), 57-73. http://dx.doi.org/10.2174/1871520617666170918143911 PMID: 28925877

[25] Kumar, D.; Sharma, P.; Nepali, K.; Mahajan, G.; Mintoo, M.J.; Singh, A.; Singh, G.; Mondhe, D.M.; Singh, G.; Jain, S.K.; Gupta, G.K.; Ntie-Kang, F. Antitumour, acute toxicity and molecular modeling studies of 4-(pyridin-4-yl)-6-(thiophen-2-yl) pyrimidin-2(1H)-one against Ehrlich ascites carcinoma and sarcoma-180. *Heliyon*, **2018**, *4*(6), e00661. http://dx.doi.org/10.1016/j.heliyon.2018.e00661 PMID: 30003157

[26] Kumar, D.; Nepali, K.; Bedi, P.M.S.; Kumar, S.; Malik, F.; Jain, S. 4,6-diaryl pyrimidones as constrained chalcone analogues: Design, Synthesis and Evaluation as anti-proliferative agents. *Anticancer. Agents Med. Chem.*, **2015**, *15*(6), 793-803. http://dx.doi.org/10.2174/1871520615666150318101436 PMID: 25783964

[27] Kumar, D.; Singh, O.; Nepali, K.; Bedi, P.; Qayum, A.; Singh, S.; Jain, S.K. Naphthoflavones as antiproliferative agents: design, synthesis and biological evaluation. *Anticancer. Agents Med. Chem.*, **2016**, *16*(7), 881-890. http://dx.doi.org/10.2174/1871520616666160204113536 PMID: 26845133

[28] Jain, V.; Verma, S.K. Folkloric use of plants for treatment of epilepsy in India. *J. Trad. Folk Pract.*, **2016**, *2*(3), 120-134.

[29] Jain, S.K. *Dictionary of Indian folk medicine and Ethnobotany*; New Delhi, **1991**, pp. 46-51.

[30] Amjad, M.S.; Arshad, M.; Saboor, A.; Page, S.; Chaudhari, S.K. Ethnobotanical profiling of the medicinal flora of Kotli, Azad Jammu and Kashmir, Pakistan: Empirical reflections on multinomial logit specifications. *Asian Pac. J. Trop. Med.*, **2017**, *10*(5), 503-514.
http://dx.doi.org/10.1016/j.apjtm.2017.05.008 PMID: 28647189

[31] Shirsat, R.; Suradkar, S.; Koche, D. Some phenolic compounds of *Salvia plebeian. J. Biosci. Discov.*, **2012**, *3*, 61-63.

[32] Mahapatra, S.K.; Mookerjee, M.; Roy, D.S.; Karak, P.; Das, S.; Dastidar, S.G. Evaluation of antimicrobial potentiality of a flavonoid, isolated from the leaf of the plant *Colebrookea oppositifolia*. *Int. J. Biological. Pharm. Res.*, **2013**, *4*, 225-230.

[33] Akhtar, N.; Haq, I.; Mirza, B. Phytochemical analysis and comprehensive evaluation of antimicrobial and antioxidant properties of 61 medicinal plant species. *Arab. J. Chem.*, **2015**, *7*, 98-105.
http://dx.doi.org/10.1016/j.arabjc.2015.01.013

[34] Bhatia, H.; Sharma, Y.P.; Manhas, R.K.; Kumar, K. Ethnomedicinal plants used by the villagers of district Udhampur, J&K, India. *J. Ethnopharmacol.*, **2014**, *151*(2), 1005-1018.
http://dx.doi.org/10.1016/j.jep.2013.12.017 PMID: 24365639

[35] Pandey, A.K.; Tripathi, N.N. Diversity and distribution of aromatic plants in forests of Gorakhpur division, U.P. *India. Bio. Forum Int. J.*, **2010**, *2*, 25-33.

[36] Manandhar, N.P. An inventory of some herbal drugs of Myagdi district, Nepal. *Econ. Bot.*, **1995**, *49*(4), 371-379.
http://dx.doi.org/10.1007/BF02863087

[37] Paul, S.R. Medicinal Plants of Netarhat, Bihar (India). *Q. J. Crude Drug Res.*, **1977**, *15*(2), 79-97.
http://dx.doi.org/10.3109/13880207709081926

[38] Ghaisas, M.M.; Sharma, S.; Ganu, G.P.; Limaye, R.P. Antiulcer activity of *Colebrookea oppositifolia. Res. J. Pharmcol. Pharmacod.*, **2010**, *2*, 66-70.

[39] Venkateshappa, S.M.; Sreenath, K.P. Potential medicinal plants of Lamiaceae. *Am. Int. J. Res. Form. App. Nat. Sci.*, **2013**, *3*, 82-87.

[40] Joshi, K.; Joshi, R.; Joshi, A.R. Indigenous knowledge and uses of medicinal plants in Macchegaun, Nepal. *Indian J. Trad. Med.*, **2011**, *10*, 281-286.

[41] Gupta, R.S.; Yadav, R.K.; Dixit, V.P.; Dobhal, M.P. Antispermatogenic effects of *Nyctanthes arbortristis* in male albino rats. *Fitoterapia*, **2001**, *72*, 70.

[42] Singh, S.P.; Singh, S.K.; Tripathi, S.C. Anitfungal activity of essential oils of some Labiatae plants against dermatophytes. *Indian Perfume.*, **1983**, *27*, 171-173.

[43] Raj, V.; Kumar, V.; Sharma, S.K.; Kumar, S.; Riyaz, M.; Kumar, A.; Singh, S. *In vitro* antimicrobial activity of *Colebrookea oppositifolia* leaf. *Int. J. Pharm. Integr. Life Sci.*, **2013**, *1*, 124-139.

[44] Verma, S.K.; Pareek, D.; Singhal, R.; Chauhan, A.K.; Parashar, P.; Dobhal, M.P. Ferulic acid ester from *Colebrookea oppositiflia. Indian J. Chem.*, **2012**, *51*, 1502-1503.

[45] Ansari, S.; Dobhal, M.P.; Tyagi, R.P.; Joshi, B.C.; Barar, F.S.K. Chemical investigation and pharmacological screening of the roots of *Colebrookia oppositifolia* Smith. *Pharmazie*, **1982**, *37*(1), 70.
PMID: 7071115

[46] McCarthy, F.O.; Chopra, J.; Ford, A.; Hogan, S.A.; Kerry, J.P.; O'Brien, N.M.; Ryan, E.; Maguire, A.R. Synthesis, isolation and characterisation of β-sitosterol and β-sitosterol oxide derivatives. *Org. Biomol. Chem.*, **2005**, *3*(16), 3059-3065.
http://dx.doi.org/10.1039/b505069c PMID: 16186940

[47] Patwardhan, S.A.; Gupta, A.S. Two new flavones from *Colebrookea oppositifolia. Indian J. Chem.*, **1981**, *20*, 627-635.

[48] Baskar, A.A.; Ignacimuthu, S.; Paulraj, G.M.; Al Numair, K.S. Chemopreventive potential of β-Sitosterol in experimental colon cancer model - an *in vitro* and *in vivo* study. *BMC Complement. Altern. Med.*, **2010**, *10*(1), 24-31.
http://dx.doi.org/10.1186/1472-6882-10-24 PMID: 20525330

[49] Morales, G.; Sierra, P.; Mancilla, A.; Paredes, A.; Loyola, L.A.; Gallardo, O.; Borquez, J. Secondary metabolites from four medicinal plants from northern chile: antimicrobial activity and biotoxicity against *Artemia salina. J. Chil. Chem. Soc.*, **2003**, *48*(2), 48-56.
http://dx.doi.org/10.4067/S0717-97072003000200002

[50] Mukherjee, P.K.; Mukherjee, K.; Lokkerbol, A.C.J.H. Flavonoid content of *Eupatoriuum glandulosum* and *Colebrookea oppositifolia. J. Nat. Rem.*, **2001**, *1*, 21-24.
http://dx.doi.org/10.18311/jnr/2001/56

[51] Aziz, S.A.; Siddiqui, S.A.; Zaman, A. Flavones from *Colebrookea oppositifolia. Indian J. Chem.*, **1974**, *12*, 1327-1328.

[52] Fan Yang, ; Xing-Cong Li, ; Han-Qing Wang, ; Chong-Ren Yang, Flavonoid glycosides from *Colebrookea oppositifolia. Phytochemistry*, **1996**, *42*(3), 867-869.
http://dx.doi.org/10.1016/0031-9422(95)00975-2

[53] Viswanatha, G.L.; Shylaja, H.; Kumar, H.Y.; Venkataranganna, M.V.; Prasad, N.B.L. Traditional uses, phytochemistry, and ethnopharmacology of *Colebrookea oppositifolia* Smith: a mini-review. *Adv. Tradition. Med.*, **2021**, *21*(2), 209-229.
http://dx.doi.org/10.1007/s13596-020-00513-y

[54] Tyagi, S.; Saraf, S.; Ojha, A.C.; Rawat, G.S. Chemical investigation of some medicinal plants of Shiwalik. *Asian J. Chem.*, **1995**, *7*, 165-170.

[55] Gaydou, E.M.; Bianchini, J.P. Etudes de composes flavoniques. I. Syntheses prosperities (UV, RMN du 13C) de quelques flavones. *Bull. Soc. Chim. Fr.*, **1978**, *1*(2), 43-47.

[56] Öksüz, S.; Halfon, B.; Terem, B. Flavonoids of *Centaurea cuneifolia*. *Plant Med.*, **1988**, *54*(1), 89.
http://dx.doi.org/10.1055/s-2006-962352 PMID: 17265218

[57] Joshi, A.R.; Joshi, K. Indigenous knowledge and uses of medicinal plants by local communities of the Kali Gandaki Watershed Area, Nepal. *J. Ethnopharmacol.*, **2000**, *73*(1-2), 175-183.
http://dx.doi.org/10.1016/S0378-8741(00)00301-9
PMID: 11025154

[58] Sardar, P.R.; Manik, S.R. GC-MS analysis of aromatic compounds from leaves of *Colebrookea oppositifolia* Smith. *Int. J. Life Sci.*, **2017**, *5*, 241-246.

[59] Burr, G.O.; Burr, M.M.; Miller, E. On the nature and role of fatty acid essential in nutrition. *J. Biol. Chem.*, **1930**, *86*(2), 587-621.
http://dx.doi.org/10.1016/S0021-9258(20)78929-5

[60] Papamandjaris, A.A.; Macdougall, D.E.; Jones, P.J.H. Medium chain fatty acid metabolism and energy expenditure: Obesity treatment implications. *Life Sci.*, **1998**, *62*(14), 1203-1215.
http://dx.doi.org/10.1016/S0024-3205(97)01143-0 PMID: 9570335

[61] Kingsbury, K.J.; Paul, S.; Morgan, D.M. The Fatty acid composition of human deposition fat. *Botanical. J.*, **1961**, *78*, 541-550.
http://dx.doi.org/10.1042/bj0780541

[62] Shirsat, R.P.; Koche, D.K.; Suradkar, S.S.; Kokate, P.S.; Bhadange, D.G. Two bioactive compounds from leaf extracts of *Colebrookea oppositifolia* Smith. *Indian J. Applied Pure Bio.*, **2014**, *29*, 61-65.

[63] Kumar, D.; Sharma, P.; Mahajan, A.; Dhawan, R.; Dua, K. Pharmaceutical interest of *in-silico* approaches. *Physical Sci. Rev.*, **2022**, pp. 1-14.
https://doi.org/10.1515/psr-2018-0157.

[64] Kumar, D.; Kumar, S.; Sharma, P.; Shri, R. Mechanistic insights and docking studies of phytomolecules as potential candidates in the management of cancer. *Curr. Pharm. Des.*, **2022**, *28*(33), 2704-2724.
http://dx.doi.org/10.2174/1381612828666220426112116
PMID: 35473540

[65] Chinchansure, A.; Arkile, M.; Shinde, D.; Sarkar, D.; Joshi, S. A new dinor-cis-labdane diterpene and flavonoids with anti-mycobacterium activity from *Colebrookea oppositifolia. Plant. Med. Lett.*, **2016**, *3*(1), e20-e24.
http://dx.doi.org/10.1055/s-0042-102200

[66] Su, B.N.; Jung Park, E.; Vigo, J.S.; Graham, J.G.; Cabieses, F.; Fong, H.H.S.; Pezzuto, J.M.; Kinghorn, A.D. Activity-guided isolation of the chemical constituents of *Muntingia calabura* using a quinone reductase induction assay. *Phytochemistry*, **2003**, *63*(3), 335-341.
http://dx.doi.org/10.1016/S0031-9422(03)00112-2
PMID: 12737982

[67] Chen, G.Y.; Dai, C.Y.; Wang, T.S.; Jiang, C.W.; Han, C.R.; Song, X.P. A new flavonol from the stem-bark of *Premna fulva. ARKIVOC*, **2010**, *2010*(2), 179-185.
http://dx.doi.org/10.3998/ark.5550190.0011.213

[68] Asakawa, Y. Chemical constituents of *Alnus sieboldiana* (Betulaceae) II. The isolation and structure of flavonoids and stilbenes. *Bull. Chem. Soc.*, **1971**, *44*, 2761-2766.

[69] Iinuma, M.; Matsuura, S.; Kusuda, K. 13C-nuclear magnetic resonance (NMR) spectral studies on polysubstituted flavonoids. I. 13C-NMR spectra of flavones. *Chem. Pharm. Bull. (Tokyo)*, **1980**, *28*(3), 708-716. http://dx.doi.org/10.1248/cpb.28.708

[70] Wei, Y.; Gao, Y.; Zhang, K.; Ito, Y. Isolation of caffeic acid from Eupatorium adenophorum Spreng by high-speed counter current chromatography and synthesis of caffeic acid-intercalated layered double hydroxide. *J. Liq. Chromatogr. Relat. Technol.*, **2010**, *33*(6), 837-845. http://dx.doi.org/10.1080/10826071003684471 PMID: 20454592

[71] Williams, C.A.; Hoult, J.R.S.; Harborne, J.B.; Greenham, J.; Eagles, J. A biologically active lipophilic flavonol from *Tanacetum parthenium*. *Phytochemistry*, **1995**, *38*(1), 267-270. http://dx.doi.org/10.1016/0031-9422(94)00609-W PMID: 7766058

[72] Panichpol, K.; Waterman, P.G. Novel flavonoids from the stem of *Popowia cauliflora*. *Phytochemistry*, **1978**, *17*(8), 1363-1367. http://dx.doi.org/10.1016/S0031-9422(00)94590-4

[73] Yang, M.; Xu, X.; Xie, C.; Huang, J.; Xie, Z.; Yang, D. Isolation and purification of forsythoside A and suspensaside A from Forsythia suspensa by highspeed counter-current chromatography. *J. Liq. Chromatogr. Relat. Technol.*, **2013**, *36*, 2895-2904.

[74] Rao, L.J.M.; Kumari, G.N.K.; Rao, N.S.P. Anisofolin-A, a new acylated flavone glucoside from *Anisomeles ovata* R. *Br. Heterocycles*, **1982**, *19*, 1655-1661. http://dx.doi.org/10.3987/R-1982-09-1655

[75] Sabina, H.; Aliya, R. Bioactive assessment of selected marine red algae against Leishmania major and chemical constituents of *Osmundea pinnatifida*. *Pak. J. Bot.*, **2011**, *43*, 3053-3056.

[76] Švehlíková, V.; Bennett, R.N.; Mellon, F.A.; Needs, P.W.; Piacente, S.; Kroon, P.A.; Bao, Y. Isolation, identification and stability of acylated derivatives of apigenin 7-O-glucoside from chamomile (*Chamomilla recutita* [L.] Rauschert). *Phytochemistry*, **2004**, *65*(16), 2323-2332. http://dx.doi.org/10.1016/j.phytochem.2004.07.011 PMID: 15381003

[77] Ali, I.; Sharma, P.; Suri, K.A.; Satti, N.K.; Dutt, P.; Afrin, F.; Khan, I.A. *In vitro* antifungal activities of amphotericin B in combination with acteoside, a phenylethanoid glycoside from *Colebrookea oppositifolia*. *J. Med. Microbiol.*, **2011**, *60*(9), 1326-1336. http://dx.doi.org/10.1099/jmm.0.031906-0 PMID: 21474610

[78] Viswanatha, G.L.; Venkataranganna, M.V.; Prasad, N.B.L. Ameliorative potential of *Colebrookea oppositifolia* methanolic root extract against experimental models of epilepsy: Possible role of GABA mediated mechanism. *Biomed. Pharmacother.*, **2017**, *90*, 455-465. http://dx.doi.org/10.1016/j.biopha.2017.03.078 PMID: 28391167

[79] Brodie, M.J.; Besag, F.; Ettinger, A.B.; Mula, M.; Gobbi, G.; Comai, S.; Aldenkamp, A.P.; Steinhoff, B.J. Epilepsy, antiepileptic drugs, and aggression: an evidence-based review. *Pharmacol. Rev.*, **2016**, *68*(3), 563-602. http://dx.doi.org/10.1124/pr.115.012021 PMID: 27255267

[80] Viswanatha, G.L.; Sowmya, G.P.; Hanumanthappa, S.; Yogananda, M. Methanolic stem extract of *Colebrookea oppositifolia* attenuates epilepsy in experimental animal models: possible role of GABA pathways. *J. Biol. Active Prod. Nat.*, **2020**, *10*(1), 44-58. a

[81] Bell, G.S.; Neligan, A.; Sander, J.W. An unknown quantity-The worldwide prevalence of epilepsy. *Epilepsia*, **2014**, *55*(7), 958-962. http://dx.doi.org/10.1111/epi.12605 PMID: 24964732

[82] Goldenberg, M.M. Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment. *PT*, **2010**, *35*(7), 392-415. PMID: 20689626

[83] Hamed, S.A. The effect of epilepsy and antiepileptic drugs on sexual, reproductive and gonadal health of adults with epilepsy. *Expert Rev. Clin. Pharmacol.*, **2016**, *9*(6), 807-819. http://dx.doi.org/10.1586/17512433.2016.1160777 PMID: 26934627

[84] Mula, M. Third generation antiepileptic drug monotherapies in adults with epilepsy. *Expert Rev. Neurother.*, **2016**, *16*(9), 1087-1092. http://dx.doi.org/10.1080/14737175.2016.1195264 PMID: 27248204

[85] Yang, Y.; Wang, X. Sexual dysfunction related to antiepileptic drugs in patients with epilepsy. *Expert Opin. Drug Saf.*, **2016**, *15*(1), 31-42. http://dx.doi.org/10.1517/14740338.2016.1112376 PMID: 26559937

[86] Muazu, J.; Kaita, M.H. A review of traditional plants used in the treatment of epilepsy amongst the Hausa/Fulani tribes of northern Nigeria. *Afr. J. Tradit. Complement. Altern. Med.*, **2008**, *5*(4), 387-390. http://dx.doi.org/10.4314/ajtcam.v5i4.31294 PMID: 20161961

[87] Kritikar, K.; Basu, B. *Indian medicinal plants*; Lalit Mohan Basu, Allahabad, **2007**.

[88] Adhikari, B.S.; Babu, M.M.; Saklani, P.L.; Rawat, G.S. Distribution, use pattern and prospects for conservation of medicinal shrubs in Uttaranchal State, India. *J. Mt. Sci.*, **2007**, *4*(2), 155-180. http://dx.doi.org/10.1007/s11629-007-0155-8

[89] Yoganarasimhan, S. *Medicinal plants of India Interline Publishing Private Limited*, **1996**.

[90] Nadkarni, K. *Indian material medica.* 1976 ed.; Bombay Popular Prakashan, **1976**.

[91] Gupta, V.K.; Shukla, C.; Bisht, G.R.S.; Saikia, D.; Kumar, S.; Thakur, R.L. Detection of anti-tuberculosis activity in some folklore plants by radiometric BACTEC assay. *Lett. Appl. Microbiol.*, **2011**, *52*(1), 33-40. http://dx.doi.org/10.1111/j.1472-765X.2010.02963.x PMID: 21114505

[92] Grange, J.M.; Zumla, A. The global emergency of tuberculosis: what is the cause? *J. R. Soc. Promot. Health*, **2002**, *122*(2), 78-81. http://dx.doi.org/10.1177/146642400212200206 PMID: 12134771

[93] Sabran, S.F.; Mohamed, M.; Bakar, M.F.A. Ethnomedical knowledge of plants used for the treatment of tuberculosis in johor, malaysia. *Evid. Based Compl. Alt. Med.*, **2016**. http://dx.doi.org/10.1155/2016/2850845

[94] Matteelli, A.; Sulis, G.; Capone, S.; D'Ambrosio, L.; Migliori, G.B.; Getahun, H. Tuberculosis elimination and the challenge of latent tuberculosis. *Presse Med.*, **2017**, *46*(2), e13-e21. http://dx.doi.org/10.1016/j.lpm.2017.01.015 PMID: 28279508

[95] Said, K.; Verver, S.; Kalingonji, A.; Lwilla, F.; Mkopi, A.; Charalambous, S.; Reither, K. Tuberculosis among HIV-infected population: incidence and risk factors in rural Tanzania. *Afr. Health Sci.*, **2017**, *17*(1), 208-215. http://dx.doi.org/10.4314/ahs.v17i1.26 PMID: 29026395

[96] Sanusi, S.B.; Abu Bakar, M.F.; Mohamed, M.; Sabran, S.F.; Mainasara, M.M. Southeast asian medicinal plants as a potential source of antituberculosis agent. *Evid. Based Complement. Alternat. Med.*, **2017**, *2017*, 1-39. http://dx.doi.org/10.1155/2017/7185649 PMID: 29081822

[97] Targhotra, M.; Aggarwal, R.; Chauhan, M.K. Bioactive compounds for effective management of drug-resistant tuberculosis. *Curr. Bioact. Compd.*, **2021**, *17*(3), 196-205. http://dx.doi.org/10.2174/1573407216999200518090132

[98] Chinchansure, A.; Arkile, M.; Shukla, A.; Shanmugam, D.; Sarkar, D.; Joshi, S. *Leucas mollissima*, a source of bioactive compounds with antimalarial and antimycobacterium activities. *Plant. Med. Lett.*, **2015**, *2*(1), e35-e38. http://dx.doi.org/10.1055/s-0035-1557830

[99] Dzoyem, J.P.; Guru, S.K.; Pieme, C.A.; Kuete, V.; Sharma, A.; Khan, I.A.; Saxena, A.K.; Vishwakarma, R.A. Cytotoxic and antimicrobial activity of selected Cameroonian edible plants. *BMC Complement. Altern. Med.*, **2013**, *13*(1), 78-84. http://dx.doi.org/10.1186/1472-6882-13-78 PMID: 23565827

[100] Khan, A.; Sarkar, D. A simple whole cell based high throughput screening protocol using *Mycobacterium bovis* BCG for inhibitors against dormant and active *Tubercle bacilli*. *J. Microbiol. Methods*, **2008**, *73*(1), 62-68. http://dx.doi.org/10.1016/j.mimet.2008.01.015 PMID: 18328582

[101] Singh, U.; Akhtar, S.; Mishra, A.; Sarkar, D. A novel screening method based on menadione mediated rapid reduction of tetrazolium salt for testing of anti-mycobacterial agents. *J. Microbiol. Methods*, **2011**, *84*(2), 202-207. http://dx.doi.org/10.1016/j.mimet.2010.11.013 PMID: 21129420

[102] Fauci, A.S.; Touchette, N.A.; Folkers, G.K. Emerging infectious diseases: a 10-year perspective from the national institute of allergy and infectious diseases. *Emerg. Infect. Dis.*, **2005**, *11*(4), 519-525.

http://dx.doi.org/10.3201/eid1104.041167 PMID: 15829188

[103] Mira, A.; Simon-Soro, A.; Curtis, M.A. Role of microbial communities in the pathogenesis of periodontal diseases and caries. *J. Clin. Periodontol.*, **2017**, *44*(Suppl. 18), S23-S38. http://dx.doi.org/10.1111/jcpe.12671 PMID: 28266108

[104] van der Meulen, T.A.; Harmsen, H.J.M.; Bootsma, H.; Spijkervet, F.K.L.; Kroese, F.G.M.; Vissink, A. The microbiome-systemic diseases connection. *Oral Dis.*, **2016**, *22*(8), 719-734. http://dx.doi.org/10.1111/odi.12472 PMID: 26953630

[105] Chao, Y.; Marks, L.R.; Pettigrew, M.M.; Hakansson, A.P. *Streptococcus pneumoniae* biofilm formation and dispersion during colonization and disease. *Front. Cell. Infect. Microbiol.*, **2015**, *4*, 194-200. http://dx.doi.org/10.3389/fcimb.2014.00194 PMID: 25629011

[106] Mazumdar, K.; Ganguly, K.; Kumar, K.A.; Dutta, N.K.; Chakrabarty, A.N.; Dastidar, S.G. Antimicrobial potentiality of a new non-antibiotic: the cardiovascular drug oxyfedrine hydrochloride. *Microbiol. Res.*, **2003**, *158*(3), 259-264. http://dx.doi.org/10.1078/0944-5013-00204 PMID: 14521236

[107] Mishra, U.S.; Dutta, N.K.; Mazumdar, K.; Mahapatra, S.K.; Chakraborty, P.; Dastidar, S.G. Anti-Salmonella activity of a flavonone from *Butea frondosa* bark in mice. *Orient. Pharm. Exp. Med.*, **2008**, *8*(4), 339-348. http://dx.doi.org/10.3742/OPEM.2008.8.4.339

[108] Sushomarsi, M.S.; Pranabesh, C.; Dastidar, S.G. Potential of dopamin hydrochloride as a novel antimicrobial agent. *Int. J. Biomed. Pharm. Sci.*, **2010**, *4*, 70-75.

[109] Mazumder, R.; Dastidar, S.G.; Basu, S.P.; Mazumder, A.; Singh, S.K. Antibacterial potentiality of *Mesua ferrea* Linn. flowers. *Phytother. Res.*, **2004**, *18*(10), 824-826. http://dx.doi.org/10.1002/ptr.1572 PMID: 15551387

[110] Mishra, U.S.; Chakraborty, P.; Dasgupta, A.; Dastidar, S.G.; Martins, M.; Amaral, L. Potent bactericidal action of a flavonoid fraction isolated from the stem bark of *Butea frondosa*. *In Vivo*, **2009**, *23*(1), 29-32. PMID: 19368121

[111] Panda, S.K.; Padhi, L.; Leyssen, P.; Liu, M.; Neyts, J.; Luyten, W. Antimicrobial, anthelmintic, and antiviral activity of plants traditionally used for treating infectious diseases in the similipal biosphere reserve, Odisha, India. *Front. Pharmacol.*, **2017**, *8*, 658-667. http://dx.doi.org/10.3389/fphar.2017.00658 PMID: 29109684

[112] Sharma, V.; Sharma, H.V.; Mehta, D.; Chhabra, B.; Thakur, D.; Sourirajan, A.; Dev, K. Comparative analysis of antibacterial and antifungal properties of traditional medicinal plants of shimla and solan, himachal pradesh. *Int. J. Pharmacog. Phytochem. Res.*, **2014**, *6*, 18-26.

[113] Soman, I.; Mengi, S.A.; Kasture, S.B. Effect of leaves of *Butea frondosa* on stress, anxiety, and cognition in rats. *Pharmacol. Biochem. Behav.*, **2004**, *79*(1), 11-16. http://dx.doi.org/10.1016/j.pbb.2004.05.022 PMID: 15388278

[114] Gubarev, M.I.; Enioutina, E.Y.; Taylor, J.L.; Visic, D.M.; Daynes, R.A. Plant-derived glycoalkaloids protect mice against lethal infection with *Salmonella typhimurium*. *Phytother. Res.*, **1998**, *12*(2), 79-88. http://dx.doi.org/10.1002/(SICI)1099-1573(199803)12:2<79::AID-PTR192>3.0.CO;2-N

[115] Cowan, M.M. Plant products as antimicrobial agents. *Clin. Microbiol. Rev.*, **1999**, 564-582. http://dx.doi.org/10.1128/CMR.12.4.564

[116] Savoia, D. Plant-derived antimicrobial compounds: alternatives to antibiotics. *Future Microbiol.*, **2012**, *7*(8), 979-990. http://dx.doi.org/10.2217/fmb.12.68 PMID: 22913356

[117] Gilling, D.H.; Kitajima, M.; Torrey, J.R.; Bright, K.R. Mechanisms of antiviral action of plant antimicrobials against murine norovirus. *Appl. Environ. Microbiol.*, **2014**, *80*(16), 4898-4910. http://dx.doi.org/10.1128/AEM.00402-14 PMID: 24907316

[118] Ahmed, T.; Kanwal, R.; Hassan, M.; Ayub, N. Assessment of Antibacterial Activity of *Colebrookia oppositifolia* against Waterborne Pathogens Isolated from Drinking Water of the Pothwar Region in Pakistan. *Hum. Ecol. Risk Assess.*, **2009**, *15*(2), 401-415. http://dx.doi.org/10.1080/10807030902761510

[119] Qazi, G.N.; Suri, O.P.; Bedi, K.L.; Suri, K.A.; Gupta, B.D.; Jaggi, B.S.; Kapahi, B.K.; Satti, N.K.; Amina, M. Hepatoprotective agent of plant origin and a process thereof. United States Patent number US 6,989,162 B2, **2006**.

[120] Díaz, A.M.; Abad, M.J.; Fernández, L.; Silván, A.M.; De Santos, J.; Bermejo, P. Phenylpropanoid glycosides from *Scrophularia scorodonia*: *In vitro* anti-inflammatory activity. *Life Sci.*, **2004**, *74*(20), 2515-2526. http://dx.doi.org/10.1016/j.lfs.2003.10.008 PMID: 15010262

[121] Wu, Y.T.; Tsai, T.R.; Lin, L.C.; Tsai, T.H. Liquid chromatographic method with amperometric detection to determine acteoside in rat blood and brain microdialysates and its application to pharmacokinetic study. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.*, **2007**, *853*(1-2), 281-286. http://dx.doi.org/10.1016/j.jchromb.2007.03.033 PMID: 17442636

[122] Li, L.; Tsao, R.; Yang, R.; Liu, C.; Young, J.C.; Zhu, H. Isolation and purification of phenylethanoid glycosides from *Cistanche deserticola* by high-speed counter-current chromatography. *Food Chem.*, **2008**, *108*(2), 702-710. http://dx.doi.org/10.1016/j.foodchem.2007.10.082 PMID: 26059151

[123] Ramage, G.; Vande Walle, K.; Wickes, B.L.; Lopez-Ribot, J.L. Standardized method for *in vitro* antifungal susceptibility testing of *Candida albicans* biofilms. *Antimicrob. Agents Chemother.*, **2001**, *45*, 2475-2479. http://dx.doi.org/10.1128/AAC.45.9.2475-2479.2001

[124] Martinez, L.R.; Casadevall, A. Susceptibility of *Cryptococcus neoformans* biofilms to antifungal agents *in vitro*. *Antimicrob. Agents Chemother.*, **2006**, *50*(3), 1021-1033. http://dx.doi.org/10.1128/AAC.50.3.1021-1033.2006 PMID: 16495265

[125] Mowat, E.; Butcher, J.; Lang, S.; Williams, C.; Ramage, G. Development of a simple model for studying the effects of antifungal agents on multicellular communities of *Aspergillus fumigatus*. *J. Med. Microbiol.*, **2007**, *56*(9), 1205-1212. http://dx.doi.org/10.1099/jmm.0.47247-0 PMID: 17761484

[126] Ramani, R.; Ramani, A.; Wong, S.J. Rapid flow cytometric susceptibility testing of *Candida albicans*. *J. Clin. Microbiol.*, **1997**, *35*(9), 2320-2324. http://dx.doi.org/10.1128/jcm.35.9.2320-2324.1997 PMID: 9276410

[127] Joung, Y.H.; Kim, H.R.; Lee, M.K.; Park, A.J. Fluconazole susceptibility testing of *Candida* species by flow cytometry. *J. Infect.*, **2007**, *54*(5), 504-508. http://dx.doi.org/10.1016/j.jinf.2006.09.016 PMID: 17084902

[128] Shirsat, R.; Suradkar, S.; Koche, D. Antioxidant activity and total polyphenol content of aqueous extracts from three selected lamiaceae members. *Indian J. Pharm.*, **2011**, *2*, 43-45.

[129] Yanishlieva, N.V.; Marinova, E.; Pokorný, J. Natural antioxidants from herbs and spices. *Eur. J. Lipid Sci. Technol.*, **2006**, *108*(9), 776-793. http://dx.doi.org/10.1002/ejlt.200600127

[130] Saxena, A.; Saxena, A.K.; Singh, J.; Bhushan, S. Natural antioxidants synergistically enhance the anticancer potential of AP9-cd, a novel lignan composition from *Cedrus deodara* in human leukemia HL-60 cells. *Chem. Biol. Interact.*, **2010**, *188*(3), 580-590. http://dx.doi.org/10.1016/j.cbi.2010.09.029 PMID: 20932957

[131] Andrews, F.A.; Beggs, W.H.; Sarosi, G.A. Influence of antioxidants on the bioactivity of amphotericin B. *Antimicrob. Agents Chemother.*, **1977**, *11*(4), 615-618. http://dx.doi.org/10.1128/AAC.11.4.615 PMID: 324396

[132] Beggs, W.H.; Andrews, F.A.; Sarosi, G.A. Synergistic action of amphotericin B and antioxidants against certain opportunistic yeast pathogens. *Antimicrob. Agents Chemother.*, **1978**, *13*(2), 266-270. http://dx.doi.org/10.1128/AAC.13.2.266 PMID: 348098

[133] Barman, N.R.; Paul, H.S.; Kar, P.K.; Hazam, P.K.; Nandy, S.; Tyagi, H. *In vitro* evaluation of antioxidant activity of *Colebrookea oppositifolia* Smith. *Int. J. Drug Discov. Herbal Res.*, **2012**, *2*, 296-300.

[134] Pan, N.; Hori, H. Antioxidant action of acteoside and its analogs on lipid peroxidation. *Redox Rep.*, **1996**, *2*(2), 149-154. http://dx.doi.org/10.1080/13510002.1996.11747042 PMID: 27405954

[135] Lahloub, M.; Zaghloul, A.; El-Khayaat, S.; Afifi, M.; Sticher, O. 2′-O-acetylpoliumoside: a new phenylpropanoid glycoside from *Orobanche ramosa*. *Planta Med.*, **1991**, *57*(5), 481-485.

http://dx.doi.org/10.1055/s-2006-960177 PMID: 1798805

[136] Suzuki, Y.J.; Tsuchiya, M.; Safadi, A.; Kagan, V.E.; Packer, L. Antioxidant properties of nitecapone (OR-462). *Free Radic. Biol. Med.*, **1992**, *13*(5), 517-525. http://dx.doi.org/10.1016/0891-5849(92)90146-8 PMID: 1334029

[137] Yar Khan, H.; Zubair, H.; Fahad Ullah, M.; Ahmad, A.; Mumtaz Hadi, S. A prooxidant mechanism for the anticancer and chemopreventive properties of plant polyphenols. *Curr. Drug Targets*, **2012**, *13*(14), 1738-1749. http://dx.doi.org/10.2174/138945012804545560 PMID: 23140285

[138] Gupta, R.S.; Yadav, R.K.; Dixit, V.P.; Dobhal, M.P. Antifertility studies of *Colebrookia oppositifolia* leaf extract in male rats with special reference to testicular cell population dynamics. *Fitoterapia*, **2001**, *72*(3), 236-245. http://dx.doi.org/10.1016/S0367-326X(00)00311-7 PMID: 11295299

[139] Keel, B.A.; Abney, O. Influence of bilateral cryptorchidism in the mature rat: alterations in testicular function and serum hormone levels. *Endocrinology*, **1980**, *107*(4), 1226-1233. http://dx.doi.org/10.1210/endo-107-4-1226 PMID: 6105953

[140] Steinberger, E.; French, F.S.; Hansson, V.; Ritzen, E.M.; Nayfeh, S.N. Hormonal regulation of the seminiferous tubule function. *Curr. Top. Mol. Endocrinol.*, **1975**, *2*, 337-352. http://dx.doi.org/10.1007/978-1-4613-4440-7_24 PMID: 195771

[141] Gasinska, A.; Hill, S. The effect of hyperthermia on the mouse testis. *Neoplasma*, **1990**, *37*(3), 357-366. PMID: 2370920

[142] Courot, M.; Kilgour, R.J. Endocrine control of mammalian testicular ontogenesis. *Arch. Biol. Med. Exp. (Santiago)*, **1984**, *17*(3-4), 249-255. PMID: 6100812

[143] Monet-Kuntz, C.; Reviers, M-T.H.; Terqui, M. Variations in testicular androgen receptors and histology of the lamb testis from birth to puberty. *Reproduction*, **1984**, *70*(1), 203-210. http://dx.doi.org/10.1530/jrf.0.0700203 PMID: 6694138

[144] Østergaard, L.; Engedal, T.S.; Moreton, F.; Hansen, M.B.; Wardlaw, J.M.; Dalkara, T.; Markus, H.S.; Muir, K.W. Cerebral small vessel disease: Capillary pathways to stroke and cognitive decline. *J. Cereb. Blood Flow Metab.*, **2016**, *36*(2), 302-325. http://dx.doi.org/10.1177/0271678X15606723 PMID: 26661176

[145] Rodrigo, R.; Fernández-Gajardo, R.; Gutiérrez, R.; Matamala, J.; Carrasco, R.; Miranda-Merchak, A.; Feuerhake, W. Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. *CNS Neurol. Disord. Drug Targets*, **2013**, *12*(5), 698-714. http://dx.doi.org/10.2174/18715273113120500015 PMID: 23469845

[146] Randolph, S.A. Ischemic Stroke. *Workplace Health Saf.*, **2016**, *64*(9), 444-461. http://dx.doi.org/10.1177/2165079916665400 PMID: 27621261

[147] Katzan, I.L.; Thompson, N.R.; Uchino, K.; Lapin, B. The most affected health domains after ischemic stroke. *Neurology*, **2018**, *90*(16), e1364-e1371. http://dx.doi.org/10.1212/WNL.0000000000005327 PMID: 29592886

[148] Guzik, A.; Bushnell, C. Stroke epidemiology and risk factor management. *Continuum (Minneap. Minn.)*, **2017**, *23*(1), 15-39. http://dx.doi.org/10.1212/CON.0000000000000416 PMID: 28157742

[149] Holodinsky, J.K.; Yu, A.Y.X.; Assis, Z.A.; Al Sultan, A.S.; Menon, B.K.; Demchuk, A.M.; Goyal, M.; Hill, M.D. History, evolution, and importance of emergency endovascular treatment of acute ischemic stroke. *Curr. Neurol. Neurosci. Rep.*, **2016**, *16*(5), 42-51. http://dx.doi.org/10.1007/s11910-016-0646-5 PMID: 27021771

[150] Grupke, S.; Hall, J.; Dobbs, M.; Bix, G.J.; Fraser, J.F. Understanding history, and not repeating it. Neuroprotection for acute ischemic stroke: From review to preview. *Clin. Neurol. Neurosurg.*, **2015**, *129*, 1-9. http://dx.doi.org/10.1016/j.clineuro.2014.11.013 PMID: 25497127

[151] Durukan, A.; Tatlisumak, T. Acute ischemic stroke: Overview of major experimental rodent models, pathophysiology, and therapy of focal cerebral ischemia. *Pharmacol. Biochem. Behav.*, **2007**, *87*(1), 179-197. http://dx.doi.org/10.1016/j.pbb.2007.04.015 PMID: 17521716

[152] Fisher, M. New approaches to neuroprotective drug development. *Stroke*, **2011**, *42*(Suppl. 1), S24-S27. http://dx.doi.org/10.1161/STROKEAHA.110.592394 PMID: 21164111

[153] Jung, S.Y.; Kim, K.M.; Cho, S.; Lim, S.; Lim, C.; Kim, Y.K. Effects of pretreatment with methanol extract of *Peucedani radix* on transient ischemic brain injury in mice. *Chin. Med.*, **2017**, *12*(1), 30-35. http://dx.doi.org/10.1186/s13020-017-0151-z PMID: 29090015

[154] Bora, K.S.; Sharma, A. Neuroprotective effect of *Artemisia absinthium* L. on focal ischemia and reperfusion-induced cerebral injury. *J. Ethnopharmacol.*, **2010**, *129*(3), 403-409. http://dx.doi.org/10.1016/j.jep.2010.04.030 PMID: 20435123

[155] Sundaram, R.S.; Gowtham, L.; Rajesh, R.; Rajan, D.S.; Srinivasan, R.; Gaurav, G. Evaluation of protective role of *Ocimum sanctum* leaf extract in excitotoxicity-induced neurobehavioral deficits based on specific changes in the structure of feeding behavior, diuretic and anxiety paradigms in female rats. *J. Med. Sci. (Faisalabad, Pak.)*, **2013**, *13*(3), 182-192. http://dx.doi.org/10.3923/jms.2013.182.192

[156] Godinho, J.; de Oliveira, R.M.W.; de Sa-Nakanishi, A.B.; Bacarin, C.C.; Huzita, C.H.; Longhini, R.; Mello, J.C.P.; Nakamura, C.V.; Previdelli, I.S.; Dal Molin Ribeiro, M.H.; Milani, H.; Milani, H. Ethyl-acetate fraction of *Trichilia catigua* restores long-term retrograde memory and reduces oxidative stress and inflammation after global cerebral ischemia in rats. *Behav. Brain Res.*, **2018**, *337*, 173-182. http://dx.doi.org/10.1016/j.bbr.2017.08.050 PMID: 28919157

[157] Rodrigues, F.T.S.; de Sousa, C.N.S.; Ximenes, N.C.; Almeida, A.B.; Cabral, L.M.; Patrocínio, C.F.V.; Silva, A.H.; Leal, L.K.A.M.; Honório Júnior, J.E.R.; Macedo, D.; Vasconcelos, S.M.M. Effects of standard ethanolic extract from *Erythrina velutina* in acute cerebral ischemia in mice. *Biomed. Pharmacother.*, **2017**, *96*, 1230-1239. http://dx.doi.org/10.1016/j.biopha.2017.11.093 PMID: 29174035

[158] Yu, Z.H.; Cai, M.; Xiang, J.; Zhang, Z.N.; Zhang, J.S.; Song, X.L.; Zhang, W.; Bao, J.; Li, W.W.; Cai, D.F. PI3K/Akt pathway contributes to neuroprotective effect of Tongxinluo against focal cerebral ischemia and reperfusion injury in rats. *J. Ethnopharmacol.*, **2016**, *181*, 8-19. http://dx.doi.org/10.1016/j.jep.2016.01.028 PMID: 26805466

[159] Cui, H.J.; Yang, A.L.; Zhou, H.J.; Wang, C.; Luo, J.K.; Lin, Y.; Zong, Y.X.; Tang, T. Buyang huanwu decoction promotes angiogenesis *via* vascular endothelial growth factor receptor-2 activation through the PI3K/Akt pathway in a mouse model of intracerebral hemorrhage. *BMC Complement. Altern. Med.*, **2015**, *15*(1), 91-98. http://dx.doi.org/10.1186/s12906-015-0605-8 PMID: 25886469

[160] Viswanatha, G.L.; Sharath Kumar, L.M.; Rafiq, M.; Kavya, K.J.; Thippeswamy, A.H.; Chandrashekarappa Yuvaraj, H.; Azeemuddin, M.; Anturlikar, S.D.; Patki, P.S.; Babu, U.V.; Ramakrishnan, S. LC-MS/MS profiling and neuroprotective effects of Mentat® against transient global ischemia and reperfusion–induced brain injury in rats. *Nutrition*, **2015**, *31*(7-8), 1008-1017. http://dx.doi.org/10.1016/j.nut.2015.02.009 PMID: 26059376

[161] Xiang, J.; Tang, Y.P.; Wu, P.; Gao, J.P.; Cai, D.F. Chinese medicine Nao-Shuan-Tong attenuates cerebral ischemic injury by inhibiting apoptosis in a rat model of stroke. *J. Ethnopharmacol.*, **2010**, *131*(1), 174-181. http://dx.doi.org/10.1016/j.jep.2010.06.021 PMID: 20600767

[162] Ren, C.; Wang, B.; Li, N.; Jin, K.; Ji, X. Herbal formula danggui-shaoyao-san promotes neurogenesis and angiogenesis in rat following middle cerebral artery occlusion. *Aging Dis.*, **2015**, *6*(4), 245-253. http://dx.doi.org/10.14336/AD.2014.1126 PMID: 26236546

[163] Wang, H.N.; Peng, Y.; Tan, Q.R.; Wang, H.H.; Chen, Y.C.; Zhang, R.G.; Wang, Z.Z.; Guo, L.; Liu, Y.; Zhang, Z.J. Free and Easy Wanderer Plus (FEWP), a polyherbal preparation, ameliorates PTSD-like behavior and cognitive impairments in stressed rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2009**, *33*(8), 1458-1463. http://dx.doi.org/10.1016/j.pnpbp.2009.07.031 PMID: 19665511

[164] Sun, K.; Hu, Q.; Zhou, C.M.; Xu, X.S.; Wang, F.; Hu, B.H.; Zhao, X.Y.; Chang, X.; Chen, C.H.; Huang, P.; An, L.H.; Liu, Y.Y.; Fan, J.Y.; Wang, C.S.; Yang, L.; Han, J.Y. Cerebralcare Granule®, a

Chinese herb compound preparation, improves cerebral microcirculatory disorder and hippocampal CA1 neuron injury in gerbils after ischemia–reperfusion. *J. Ethnopharmacol.*, **2010**, *130*(2), 398-406. http://dx.doi.org/10.1016/j.jep.2010.05.030 PMID: 20580803

[165] Son, H.Y.; Jung, H.W.; Kim, W.K.; Park, Y.K. The vasoprotective effect of JP05 through the activation of PI3K/Akt-dependent eNOS and MEK/ERK pathways in brain endothelial cells. *J. Ethnopharmacol.*, **2010**, *130*(3), 607-613. http://dx.doi.org/10.1016/j.jep.2010.05.050 PMID: 20561929

[166] Takakura, S.; Sogabe, K.; Satoh, H.; Mori, J.; Fujiwara, T.; Totsuka, Z.; Tokuma, Y.; Kohsaka, M. Nilvadipine as a neuroprotective calcium entry blocker in a rat model of global cerebral ischemia. A comparative study with nicardipine hydrochloride. *Neurosci. Lett.*, **1992**, *141*(2), 199-202. http://dx.doi.org/10.1016/0304-3940(92)90894-D PMID: 1436634

[167] Hadorn, D.C. A small-animal model of cerebral ischemia: Verapamil improves neurological outcome. *Ann. Emerg. Med.*, **1984**, *13*(5), 385-386. http://dx.doi.org/10.1016/S0196-0644(84)80146-8

[168] Riaz, T.; Abbasi, M.; Shahzadi, T.; Rehman, A.; Siddiqui, S.; Ajaib, M. *Colebrookia oppositifolia*: A valuable source for natural antioxidants. *J. Med. Plants Res.*, **2011**, *5*, 4180-4187.

[169] Subba, B.; Basnet, P. Antimicrobial and antioxidant activity of some indigenous plants of Nepal. *J. Pharmacogn. Phytochem.*, **2014**, *3*, 62-67.

[170] Viswanatha, G.L.; Venkataranganna, M.V.; Prasad, N.B.L.; Hanumanthappa, S. Chemical characterization and cerebroprotective effect of methanolic root extract of *Colebrookea oppositifolia* in rats. *J. Ethnopharmacol.*, **2018**, *223*, 63-75. http://dx.doi.org/10.1016/j.jep.2018.05.009 PMID: 29777902

[171] Tsai, P.J.; Tsai, T.H.; Yu, C.H.; Ho, S.C. Evaluation of NO-suppressing activity of several Mediterranean culinary spices. *Food Chem. Toxicol.*, **2007**, *45*(3), 440-447. http://dx.doi.org/10.1016/j.fct.2006.09.006 PMID: 17074427

[172] Damiano, S.; Forino, M.; De, A.; Vitali, L.A.; Lupidi, G.; Taglialatela-Scafati, O. Antioxidant and antibiofilm activities of secondary metabolites from *Ziziphus jujuba* leaves used for infusion preparation. *Food Chem.*, **2017**, *230*, 24-29. http://dx.doi.org/10.1016/j.foodchem.2017.02.141 PMID: 28407906

[173] Pandey, M.M.; Khatoon, S.; Rastogi, S.; Rawat, A.K.S. Determination of flavonoids, polyphenols and antioxidant activity of *Tephrosia purpurea*: a seasonal study. *J. Integr. Med.*, **2016**, *14*(6), 447-455. http://dx.doi.org/10.1016/S2095-4964(16)60276-5 PMID: 27854196

[174] Benabdelaziz, I.; Marcourt, L.; Benkhaled, M.; Wolfender, J.L.; Haba, H. Antioxidant and antibacterial activities and polyphenolic constituents of *Helianthemum sessiliflorum* Pers. *Nat. Prod. Res.*, **2017**, *31*(6), 686-690. http://dx.doi.org/10.1080/14786419.2016.1209669 PMID: 27417554

[175] Smeriglio, A.; Galati, E.M.; Monforte, M.T.; Lanuzza, F.; D'Angelo, V.; Circosta, C. Polyphenolic compounds and antioxidant activity of cold-pressed seed oil from Finola cultivar of *Cannabis sativa* L. *Phytother. Res.*, **2016**, *30*(8), 1298-1307. http://dx.doi.org/10.1002/ptr.5623 PMID: 27076277

[176] Al-Rimawi, F.; Abu-Lafi, S.; Abbadi, ; Alamarneh, A.A.A.; Sawahreh, R.A.; Odeh, I. Analysis of phenolic and flavonoids of wild *Ephedra alata* plant extracts by LC/PDA and LC/MS and their antioxidant activity. *Afr. J. Tradit. Complement. Altern. Med.*, **2017**, *14*(2), 130-141. http://dx.doi.org/10.21010/ajtcam.v14i2.14 PMID: 28573229

[177] Choi, S.Y.; Ko, H.C.; Ko, S.Y.; Hwang, J.H.; Park, J.G.; Kang, S.H.; Han, S.H.; Yun, S.H.; Kim, S.J. Correlation between flavonoid content and the NO production inhibitory activity of peel extracts from various citrus fruits. *Biol. Pharm. Bull.*, **2007**, *30*(4), 772-778. http://dx.doi.org/10.1248/bpb.30.772 PMID: 17409518

[178] Conforti, F.; Menichini, F. Phenolic compounds from plants as nitric oxide production inhibitors. *Curr. Med. Chem.*, **2011**, *18*(8), 1137-1145. http://dx.doi.org/10.2174/092986711795029690 PMID: 21291370

[179] Merly, L.; Smith, S.L. Murine RAW 264.7 cell line as an immune target: are we missing something? *Immunopharmacol. Immunotoxicol.*, **2017**, *39*(2), 55-58. http://dx.doi.org/10.1080/08923973.2017.1282511 PMID: 28152640

[180] Kim, M.; Lee, S.; Ki, C.S. Cellular behavior of RAW 264.7 cells in 3D poly (ethylene glycol) hydrogel niches. *ACS Biomater. Sci. Eng.*, **2019**, *5*(2), 922-932. http://dx.doi.org/10.1021/acsbiomaterials.8b01150 PMID: 33405849

[181] Chang, K.C. Cilostazol inhibits HMGB1 release in LPS-activated RAW 264.7 cells and increases the survival of septic mice. *Thromb. Res.*, **2015**, *136*(2), 456-464. http://dx.doi.org/10.1016/j.thromres.2015.06.017 PMID: 26116490

[182] Erdogan, I.; Senol, F.S.; Sener, B. Recent approaches towards selected Lamiaceae plants for their prospective use in neuroprotection. In: *Studies in Natural Products Chemistry*; Rahman, A.U., Ed.; **012**; 38, pp. 397-415. http://dx.doi.org/10.1016/B978-0-444-59530-0.00014-9

[183] Chen, W.W.; Zhang, X.; Huang, W.J. Role of neuroinflammation in neurodegenerative diseases (Review). *Mol. Med. Rep.*, **2016**, *13*(4), 3391-3396. http://dx.doi.org/10.3892/mmr.2016.4948 PMID: 26935478

[184] Dugger, B.N.; Dickson, D.W. Pathology of neurodegenerative diseases. *Cold Spring Harb. Perspect. Biol.*, **2017**, *9*(7), a028035. http://dx.doi.org/10.1101/cshperspect.a028035 PMID: 28062563

[185] Gitler, A.D.; Dhillon, P.; Shorter, J. Neurodegenerative disease: models, mechanisms, and a new hope. *Dis. Model. Mech.*, **2017**, *10*(5), 499-502. http://dx.doi.org/10.1242/dmm.030205 PMID: 28468935

[186] Essa, M.M.; Vijayan, R.K.; Castellano-Gonzalez, G.; Memon, M.A.; Braidy, N.; Guillemin, G.J. Neuroprotective effect of natural products against Alzheimer's disease. *Neurochem. Res.*, **2012**, *37*(9), 1829-1842. http://dx.doi.org/10.1007/s11064-012-0799-9 PMID: 22614926

[187] Georgiev, M.; Alipieva, K.; Orhan, I.; Abrashev, R.; Denev, P.; Angelova, M. Antioxidant and cholinesterases inhibitory activities of *Verbascum xanthophoeniceum* Griseb. and its phenylethanoid glycosides. *Food Chem.*, **2011**, *128*(1), 100-105. http://dx.doi.org/10.1016/j.foodchem.2011.02.083 PMID: 25214335

[188] Stafford, G.I.; Pedersen, M.E.; van Staden, J.; Jäger, A.K. Review on plants with CNS-effects used in traditional South African medicine against mental diseases. *J. Ethnopharmacol.*, **2008**, *119*(3), 513-537. http://dx.doi.org/10.1016/j.jep.2008.08.010 PMID: 18775771

[189] Bondi, M.W.; Edmonds, E.C.; Salmon, D.P. Alzheimer's disease: past, present, and future. *J. Int. Neuropsychol. Soc.*, **2017**, *23*(9-10), 818-831. http://dx.doi.org/10.1017/S135561771700100X PMID: 29198280

[190] Sochocka, M.; Zwolińska, K.; Leszek, J. The infectious etiology of Alzheimer's disease. *Curr. Neuropharmacol.*, **2017**, *15*(7), 996-1009. http://dx.doi.org/10.2174/1570159X15666170313122937 PMID: 28294067

[191] Latta, C.H.; Brothers, H.M.; Wilcock, D.M. Neuroinflammation in Alzheimer's disease; A source of heterogeneity and target for personalized therapy. *Neuroscience*, **2015**, *302*, 103-111. http://dx.doi.org/10.1016/j.neuroscience.2014.09.061 PMID: 25286385

[192] Balin, B.J.; Hudson, A.P. Etiology and pathogenesis of late-onset Alzheimer's disease. *Curr. Allergy Asthma Rep.*, **2014**, *14*(3), 417-421. http://dx.doi.org/10.1007/s11882-013-0417-1 PMID: 24429902

[193] Adewusi, E.A.; Moodley, N.; Steenkamp, V. Antioxidant and acetylcholinesterase inhibitory activity of selected southern African medicinal plants. *S. Afr. J. Bot.*, **2011**, *77*(3), 638-644. http://dx.doi.org/10.1016/j.sajb.2010.12.009

[194] Tatli, I.I.; Kahraman, C.; Akdemir, Z.S. The therapeutic activities of selected Scrophulariaceae and Buddlejaceae species and their secondary metabolites against neurodegenerative diseases. *Bioactive Neutraceutical. Dietary Suppl. Neurol. Brain Dis.*, **2015**, *5*, 95-111. http://dx.doi.org/10.1016/B978-0-12-411462-3.00011-4

[195] Wang, H.; Xu, Y.; Yan, J.; Zhao, X.; Sun, X.; Zhang, Y.; Guo, J.; Zhu, C. Acteoside protects human neuroblastoma SH-SY5Y cells against β-amyloid-induced cell injury. *Brain Res.*, **2009**, *1283*, 139-147. http://dx.doi.org/10.1016/j.brainres.2009.05.101 PMID: 19520063

[196] Wang, H.Q.; Xu, Y.X.; Zhu, C.Q. Upregulation of heme oxygenase-1 by acteoside through ERK and PI3 K/Akt pathway confer neuroprotection against β-amyloid-induced neurotoxicity. *Neurotox. Res.*, **2012**, *21*(4), 368-378. http://dx.doi.org/10.1007/s12640-011-9292-5 PMID: 22147269

[197] Dharmani, P.; Kumar, K.; Shrivastava, S.; Palit, G. Ulcer healing effect of Anti-ulcer agents: A comparative study. The Internet J. *Acad. Physician Assist.*, **2003**, *3*(2), 1-7.

[198] Lanas, A.; Chan, F.K.L. Peptic ulcer disease. *Lancet*, **2017**, *390*(10094), 613-624. http://dx.doi.org/10.1016/S0140-6736(16)32404-7 PMID: 28242110

[199] Chang, S.S.; Hu, H.Y. Helicobacter pylori eradication within 120 days is associated with decreased complicated recurrent peptic ulcer bleeding patients. *Gut Liver*, **2015**, *9*(3), 346-352. http://dx.doi.org/10.5009/gnl13451 PMID: 25167793

[200] Wong, C.S.; Chia, C.F.; Lee, H.C.; Wei, P.L.; Ma, H.P.; Tsai, S.H.; Wu, C.H.; Tam, K.W. Eradication of *Helicobacter pylori* for prevention of ulcer recurrence after simple closure of perforated peptic ulcer: A meta-analysis of randomized controlled trials. *J. Surg. Res.*, **2013**, *182*(2), 219-226. http://dx.doi.org/10.1016/j.jss.2012.10.046 PMID: 23158404

[201] Chaturvedi, A.; Kumar, M.M.; Bhawani, G.; Chaturvedi, H.; Kumar, M.; Goel, R.K. Effect of ethanolic extract of *Eugenia jambolana* seeds on gastric ulceration and secretion in rats. *Indian J. Physiol. Pharmacol.*, **2007**, *51*(2), 131-140. PMID: 18175656

[202] Chung, C.S.; Chiang, T.H.; Lee, Y.C. A systematic approach for the diagnosis and treatment of idiopathic peptic ulcers. *Korean J. Intern. Med. (Korean. Assoc. Intern. Med.)*, **2015**, *30*(5), 559-570. http://dx.doi.org/10.3904/kjim.2015.30.5.559 PMID: 26354049

[203] Nguelefack, T.B.; Feumebo, C.B.; Ateufack, G.; Watcho, P.; Tatsimo, S.; Atsamo, A.D.; Tane, P.; Kamanyi, A. Anti-ulcerogenic properties of the aqueous and methanol extracts from the leaves of *Solanum torvum* Swartz (Solanaceae) in rats. *J. Ethnopharmacol.*, **2008**, *119*(1), 135-140. http://dx.doi.org/10.1016/j.jep.2008.06.008 PMID: 18602980

[204] Omar, H.; Nordin, N.; Hassandarvish, P.; Hajrezaie, M.; Azizan, A.H.S.; Fadaeinasab, M.; Abdul Majid, N.; Abdulla, M.; Mohd Hashim, N.; Mohd Ali, H. Methanol leaf extract of *Actinodaphne sesquipedalis* (Lauraceae) enhances gastric defense against ethanol-induced ulcer in rats. *Drug Des. Devel. Ther.*, **2017**, *11*, 1353-1365. http://dx.doi.org/10.2147/DDDT.S120564 PMID: 28496305

[205] Paguigan, N.D.; Castillo, D.H.; Chichioco-Hernandez, C.L. Anti-ulcer activity of leguminosae plants. *Arg. Gastroenterol.*, **2014**, *51*, 64-67.

[206] do Nascimento, R.; de Sales, I.; de Oliveira Formiga, R.; Barbosa-Filho, J.; Sobral, M.; Tavares, J.; Diniz, M.; Batista, L. Activity of alkaloids on peptic ulcer: what's new? *Molecules*, **2015**, *20*(1), 929-950. http://dx.doi.org/10.3390/molecules20010929 PMID: 25580688

[207] Wang, Y.C. Medicinal plant activity on *Helicobacter pylori* related diseases. *World J. Gastroenterol.*, **2014**, *20*(30), 10368-10382. http://dx.doi.org/10.3748/wjg.v20.i30.10368 PMID: 25132753

[208] Wang, L.; Wang, X.; Zhu, X.M.; Liu, Y.Q.; Du, W.J.; Ji, J.; He, X.; Zhang, C.F.; Li, F.; Guo, C.R.; Wang, C.Z.; Yuan, C.S. Gastroprotective effect of alkaloids from cortex phellodendri on gastric ulcers in rats through neurohumoral regulation. *Planta Med.*, **2016**, *83*(03/04), 277-284. http://dx.doi.org/10.1055/s-0042-114044 PMID: 27648555

[209] Falcão, H.S.; Mariath, I.R.; Diniz, M.F.F.M.; Batista, L.M.; Barbosa-Filho, J.M. Plants of the American continent with antiulcer activity. *Phytomedicine*, **2008**, *15*(1-2), 132-146. http://dx.doi.org/10.1016/j.phymed.2007.07.057 PMID: 17904832

[210] Dash, S. Effect of Aqueous extracts of *Colebrookea oppositifolia* on bioavailability of amoxycilline in rabbits. *Indian Drug.*, **2004**, *414*, 231-235.

[211] Repetto, M.G.; Llesuy, S.F. Antioxidant properties of natural compounds used in popular medicine for gastric ulcers. *Braz. J. Med. Biol. Res.*, **2002**, *35*(5), 523-534. http://dx.doi.org/10.1590/S0100-879X2002000500003 PMID: 12011936

[212] Goel, R.K.; Maiti, R.N. Role of endogenous eicosanoids in the antiulcer effect of kaempferol. *Fitoterapia*, **1996**, *6*, 548-552.

[213] Cadirci, E.; Suleyman, H.; Aksoy, H.; Halici, Z.; Ozgen, U.; Koc, A.; Ozturk, N. Effects of *Onosma armeniacum* root extract on ethanol-induced oxidative stress in stomach tissue of rats. *Chem. Biol. Interact.*, **2007**, *170*(1), 40-48. http://dx.doi.org/10.1016/j.cbi.2007.06.040 PMID: 17681286

[214] Barbastefano, V.; Cola, M.; Luiz-Ferreira, A.; Farias-Silva, E.; Hiruma-Lima, C.A.; Rinaldo, D.; Vilegas, W.; Souza-Brito, A.R.M. *Vernonia polyanthes* as a new source of antiulcer drugs. *Fitoterapia*, **2007**, *78*(7-8), 545-551. http://dx.doi.org/10.1016/j.fitote.2007.07.003 PMID: 17904766

[215] Shah, P.J.; Gandhi, M.S.; Shah, M.B.; Goswami, S.S.; Santani, D. Study of *Mimusops elengi* bark in experimental gastric ulcers. *J. Ethnopharmacol.*, **2003**, *89*(2-3), 305-311. http://dx.doi.org/10.1016/j.jep.2003.09.003 PMID: 14611897