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Chelidonium majus L. (Greater celandine) – A Review on its Phytochemical and Therapeutic Perspectives

Amal K. Maji, Pratim Banerji

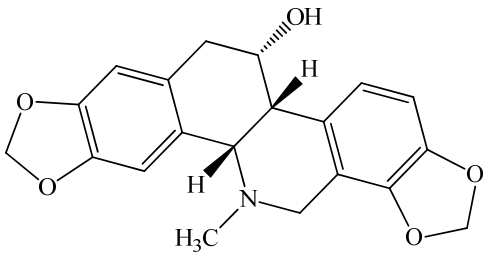
Abstract
Chelidonium majus L. (Papaveraceae) is a medicinal herb used in various traditional systems of medicine to treat ulcer, cancer, oral infection, liver disorders, chronic bronchitis, asthma, etc. Different parts of this plant contain numerous therapeutically important alkaloidal constituents such as chelidonine, chelerythrine, sanguinarine, berberine and so on. The plant and its active compounds exhibit a wide range of pharmacological activities. The plants has long history of therapeutic use in medicines without any toxic effect. Today it is one of the important components of some pharmaceutical preparations. Consumption of *C. majus* preparations possesses toxic effects on the liver although the effect becomes controversial with its hepatoprotective effect. Numerous active constituents of *C. majus* interact with various drug metabolizing enzymes that mimic possible interactions of this herb with the conventional drugs. This review provides detailed phytochemical, pharmacological and toxicological information of *C. majus* along with mechanisms of action of its various active compounds on different aspects of pharmacology. This review also highlights plausible drug interaction of its various active compounds and the future prospect of this herb.

Keywords: *C. majus*, phytochemicals, phrarmacology, toxicity and drug interactions.

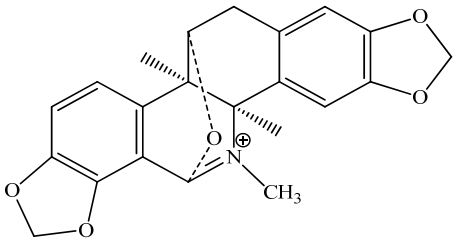
1. Introduction
Chelidonium majus (Papaveraceae) is a well-known medicinal herb distributed in Europe, Asia, and Northern Africa and is widely used against various diseases in European countries and Chinese herbal medicines [1]. It has many common names such as celandine, greater celandine, celandine poppy, elon-wort, felonwort, rock poppy, swallow-wort and tetter-wort [2]. Recently, the extract of *C. majus* was shown to be safe for the use in veterinary and human phyto-preparations [3]. In various complementary and alternative medicine (CAM) systems including homeopathy, different parts of this plant are used to treat gastric ulcer, gastric cancer, oral infection, liver diseases, general pain and various skin disorders [4]. Extracts of leaves, flower and root are internally used to stimulate the production of bile and pancreatic digestive enzymes [5]. Because of choleretic and spasmolytic properties, *C. majus* is widely used for the treatment of biliary disorders, dyspepsia, and irritable bowel syndrome [6]. In Chinese herbal medicine, it is used to treat whooping cough, blood stasis, chronic bronchitis, asthma, jaundice, gallstones and gallbladder pains and to promote diuresis in oedema and ascites [2, 7]. In homeopathic medicine, ultra-high dilutions (potencies) of *C. majus* extract are reputedly used against different forms of liver disorders including liver cancer [8]. Phytochemical analysis revealed the presence of numerous active constituents such as chelidonine, chelerythrine, sanguinarine, berberine, protopine, allocryptopine, coptisine and so on. Both, crude extract and purified constituents of *C. majus* exhibited a wide variety of pharmacological activities (anti-inflammatory, antimicrobial, immunomodulatory, anticancer, hepatoprotective, analgesic etc.) [7]. Some review articles on *C. majus* have been published previously; however none of the reviews described the complete phytochemical and pharmacological profiles of *C. majus* [7, 9, 10]. In this respect, an attempt was made to review its detailed phytochemical and pharmacological potential along with possible drug interaction potential and mechanisms of actions of the major phytochemicals on different aspects of pharmacology. To this, information about the herb was collected by online search using PubMed, Scopus, and Google scholar.

2. Phytochemicals
The therapeutic potentials of *C. majus* are related to its numerous biologically active constituents. Quantitatively the plant contains higher amount of isoquinoline alkaloids (0.27 - 2.25% in aerial parts and 3-4% in root). So far, more than 70 compounds have been isolated

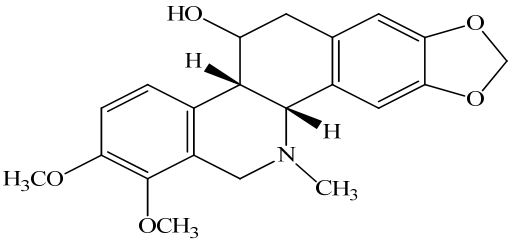
and identified from this plant including alkaloids, flavonoids, saponins, vitamins (e.g. vitamin A and C), mineral elements, sterols, acids and their derivatives [11]. Extensive phytochemical investigation revealed the presence of variety of alkaloids in different parts of this plant such as benzophenanthridines [chelidonine (**1**), didehydrochelidonine (**2**), α-homochelidonine (**3**), norchelidonine (**4**), oxychelidonine (**5**), 10-hydroxychelidonine (**6**), 10-hydroxyhomochelidonine (**7**), chelerythrine (**8**), dihydrochelerythrine (**9**), norchelerythrine (**10**), 8-hydroxydihydrochelerythrine (**11**), 8-acetonyldihydrochelerythrine (**12**), 6-methoxydihydrochelerythrine (**13**), nitidine (**14**), dihydronitidine (**15**), oxynitidine (**16**), sanguinarine (**17**), dihydrosanguinarine (**18**), norsanguinarine (**19**), oxysanguinarine (**20**), N-dimethyl-9,10-dihydroxysanguinarine (**21**), 8-hydroxydihydrosanguinarine (**22**), 6-acetonyl-5,6-dihydrosanguinarine (**23**), 6-methoxydihydrosanguinarine (**24**), methyl 2′-(7,8-dihydrosanguinarine-8-yl)acetate (**25**), chelelutine (**26**), dihydrochelelutine (**27**), chelerubine (**28**), dihydrochelerubin (**29**), chelamine (**30**), chelidimerine (**31**), chelamidine (**32**), angoline (**33**) and macarpine (**34**)], isoquinolines [noroxyhydrastinine (**35**) and turkiyenine (**36**)], protopines [protopine (**37**) and α-allocryptopine (**38**)], protoberberines [canadine (**39**), stylopine (**40**), corysamine (**41**), berberine (**42**), dihydroberberine (**43**), coptisine (**44**), dihydrocoptisine (**45**) and 8-oxycoptisine (**46**)], aporphines [magnoflorine (**47**), corydine (**48**) and norcorydine (**49**)] and quinolisidine [sparteine (**50**)] [3, 11]. In addition to these, plant also contains different aromatic and aliphatic acids such as chelidonic acid (**51**), caffeic acid (**52**), ferulic acid (**53**), *p*-coumaric acid (**54**), citric acid (**55**), malic acid (**56**), succinic acid (**57**), gentisic acid (**58**), *p*-hydroxybenzoic acid (**59**) and nicotinic acid (**60**) [11, 12]. Recently four caffeic acid esters such as 2-(-)-caffeoyl-D-glyceric acid (**61**), 4-(-)-caffeoyl-L-threonic acid (**62**), (+)-caffeoyl-L-malic acid (**63**) and 2-(-)-caffeoyl-L-threonic acid lactone (**64**) have been identified [13]. Besides, it contains lesser amount of phytosterols [α-spinasterol (**65**) and ergosterol (**66**)], polysaccharide [CM-Ala (**67**)], alcohols [1-hexacosanol (**68**), chelidoniol, and nonacosanol], flavonoids [rutin (**69**), quercetin (**70**) and kaempferol (**71**)], choline (**72**), tyramine (**73**), histamine (**74**) and saponosides [12, 14-16]. In addition to these organic compounds, 24 essential macro- and microelements including Al, As, B, Ba, Ca, Cd, Co, Cr, Cu, Fe, Hg, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, S, Ti, V and Zn have been identified in root and herb. Quantitatively, most mineral elements were between 10-65%, especially for potassium (65%) and phosphorus (54%) [17]. Chemical structures of some *C. majus* constituents are presented in Figure 1.



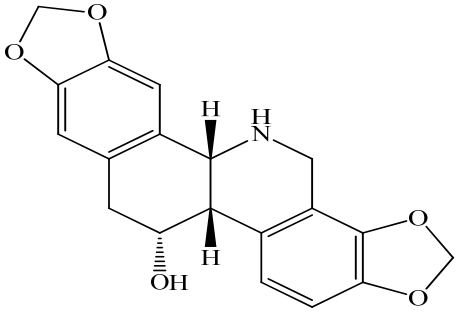
Chelidonine (1)



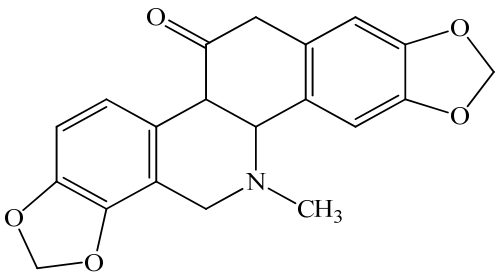
Didehydrochelidonine (2)



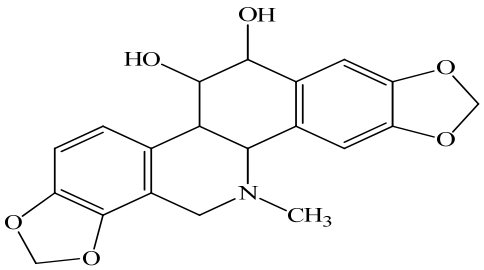
α-homochelidonine (3)



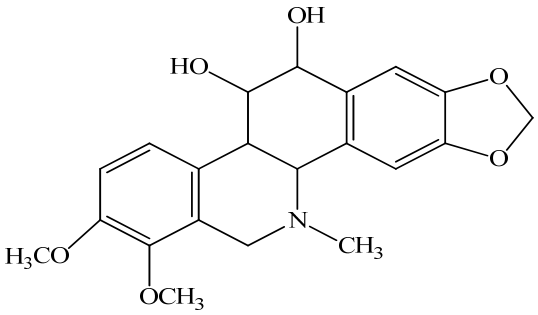
Norchelidonine (4)



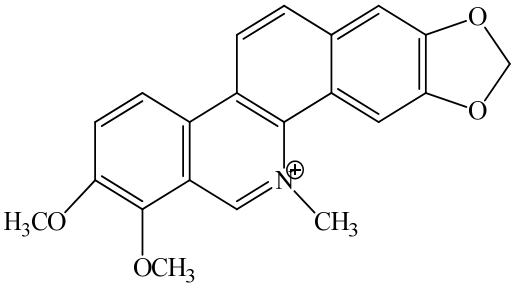
Oxychelidonine (5)



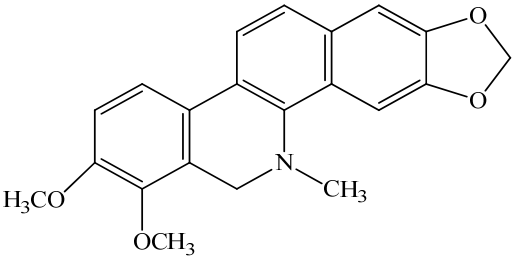
10-hydroxychelidonine (6)



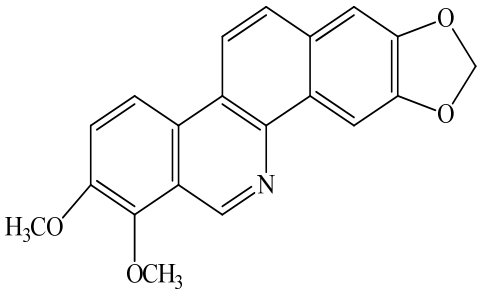
10-hydroxyhomochelidonine (7)



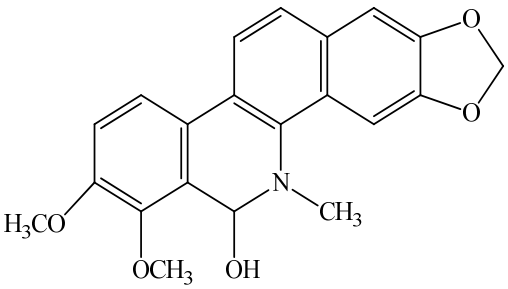
Chelerythrine (8)



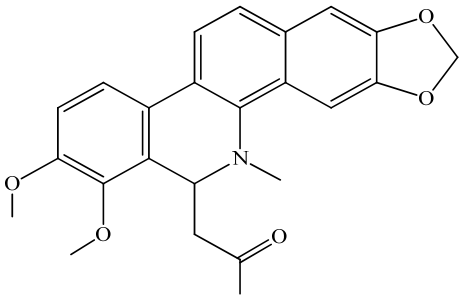
Dihydrochelerythrine (9)



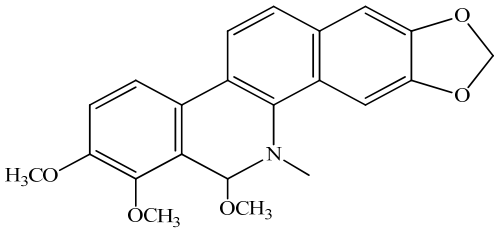
Norchelerythrine (10)



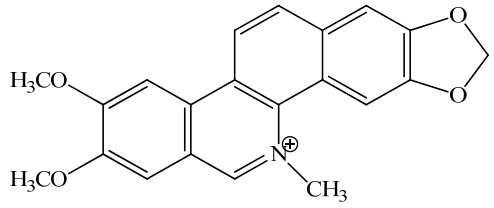
8-hydroxydihydrochelerythrine (11)



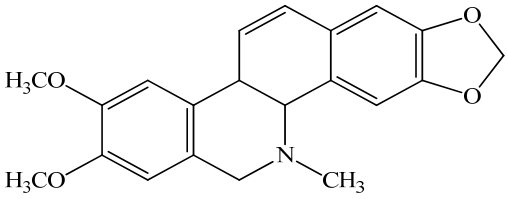
8-acetonyldihydrochelerythrine (12)



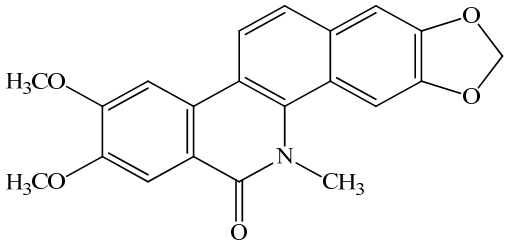
6-methoxydihydrochelerythrine (13)



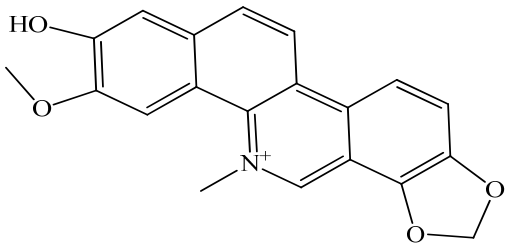
Nitidine (14)



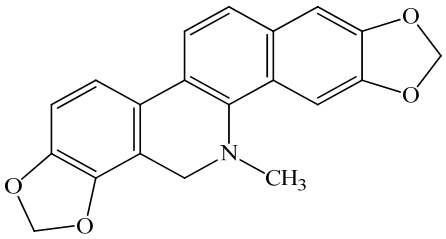
Dihydronitidine (15)



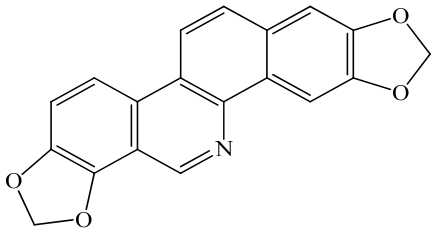
Oxynitidine (16)



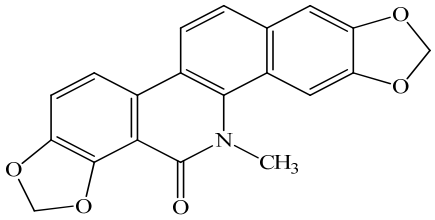
Sanguinarine (17)



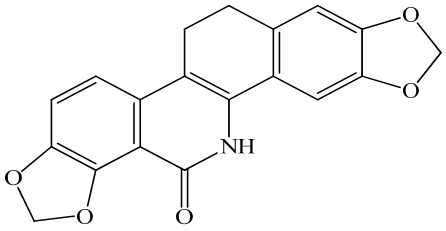
Dihydrosanguinarine (18)



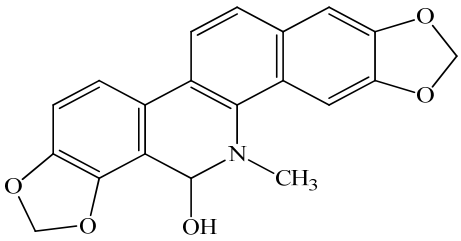
Norsanguinarine (19)



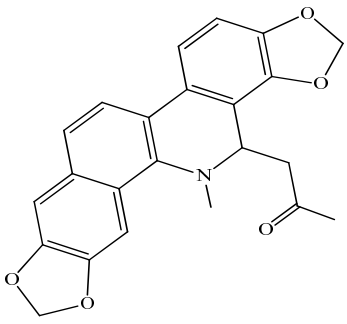
Oxysanguinarine (20)



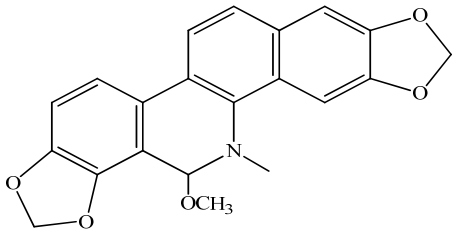
N-dimethyl-9,10- dihydroxysanguinarine (21)



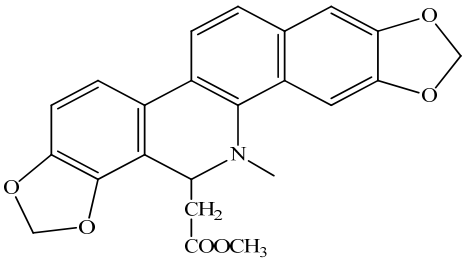
8-hydroxydihydrosanguinarine (22)



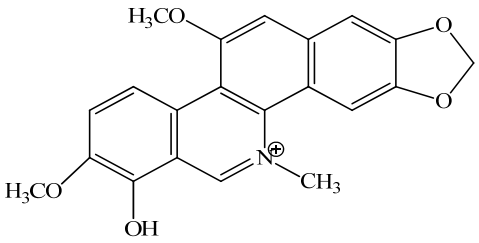
6-acetonyl-5,6-dihydrosanguinarine (23)



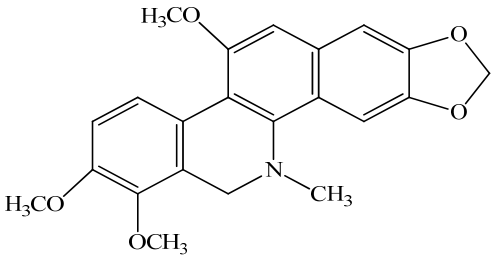
6-methoxydihydrosanguinarine (24)



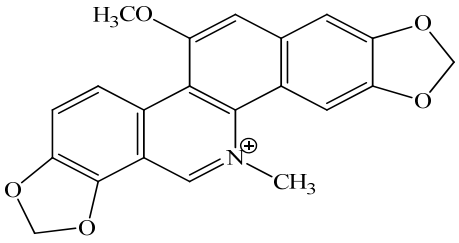
Methyl 2′-(7,8-dihydrosanguinarine-8- yl)acetate (25)



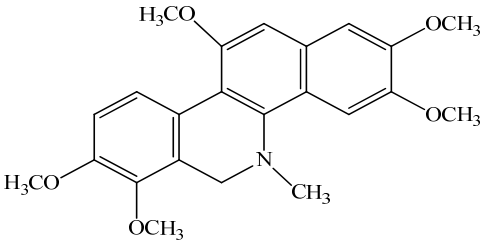
Chelelutine (26)



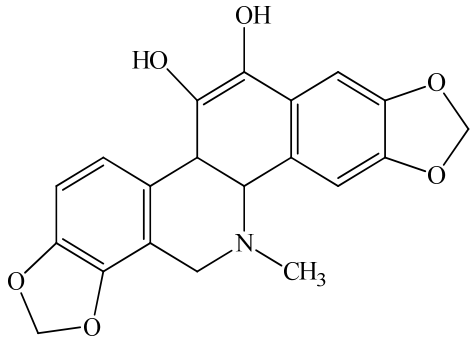
Dihydrochelelutine (27)



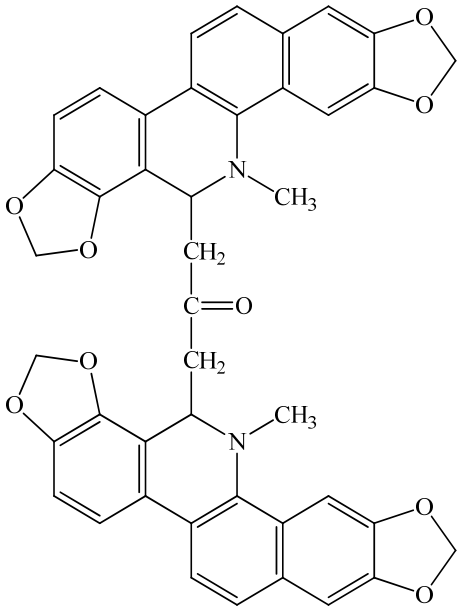
Chelerubine (28)



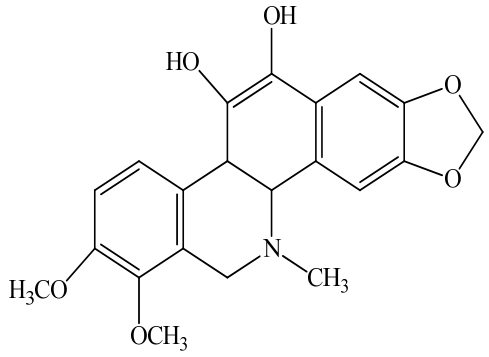
Dihydrochelerubin (29)



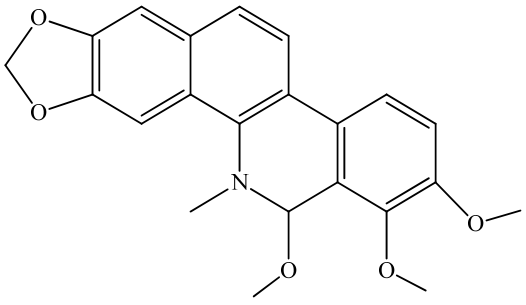
Chelamine (30)



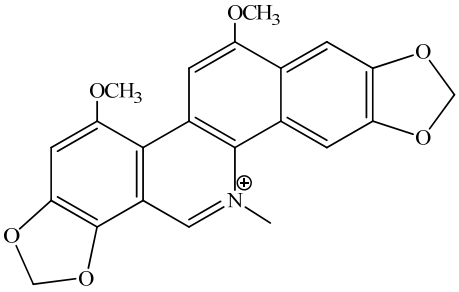
Chelidimerine (31)



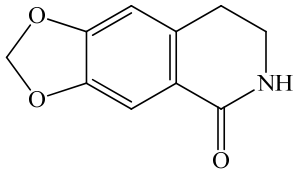
Chelamidine (32)



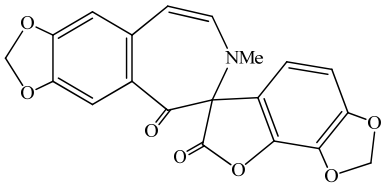
Angoline (33)



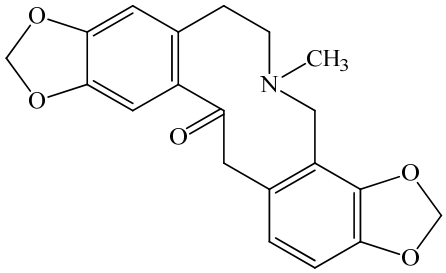
Macarpine (34)



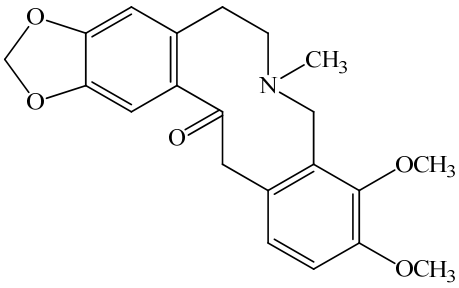
Noroxyhydrastinine (35)



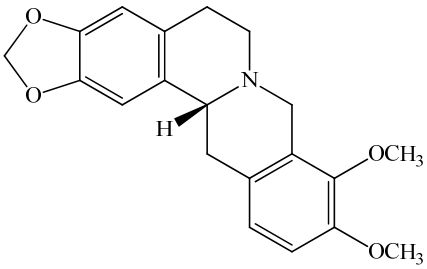
Turkiyenine (36)



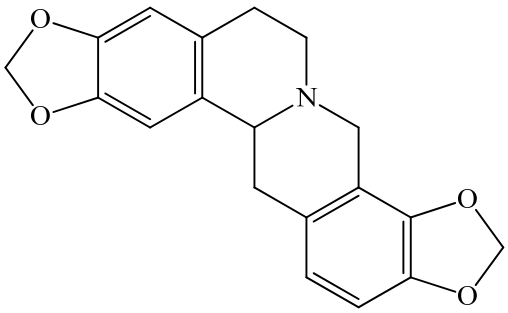
Protopine (37)



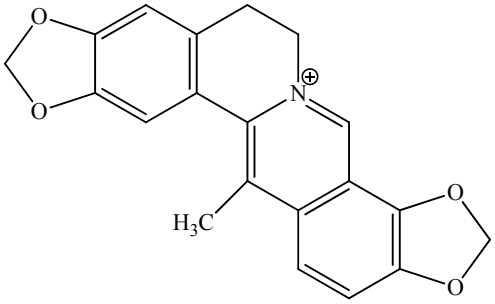
α-allocryptopine (38)



Canadine (39)



Stylopine (40)



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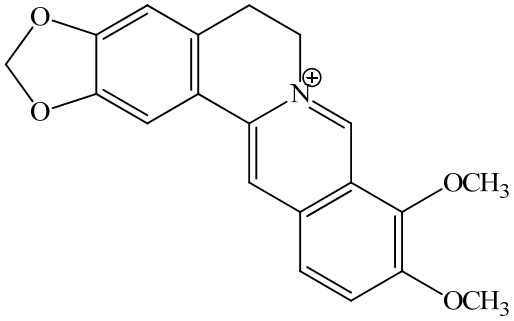
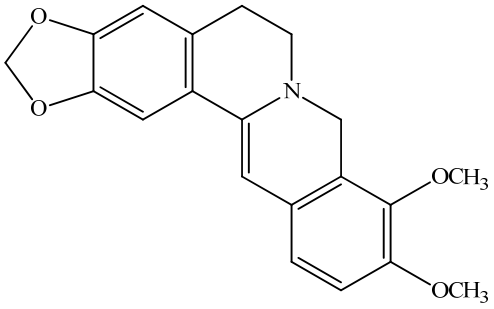
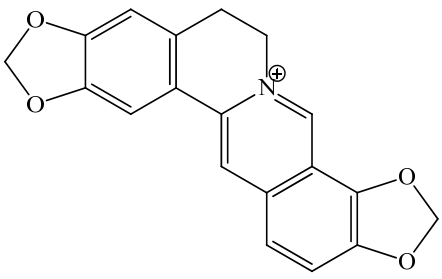


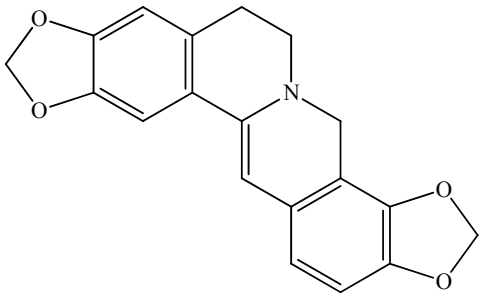
Berberine (42)



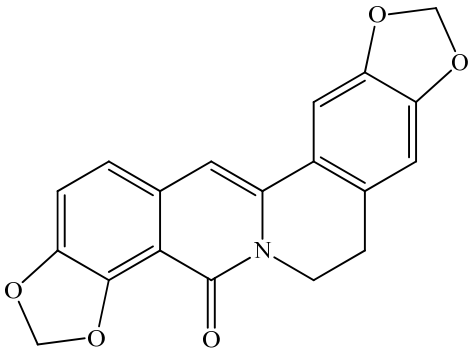
Dihydroberberine (43)



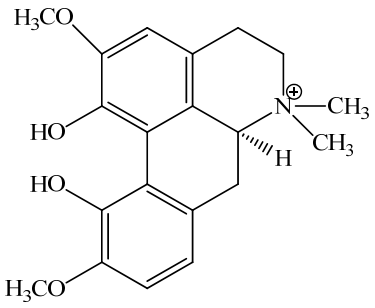
Coptisine (44)



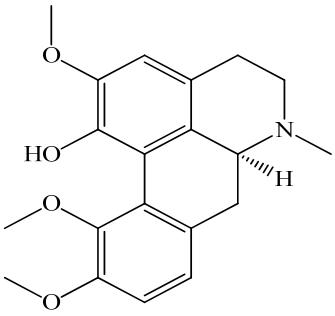
Dihydrocoptisine (45)



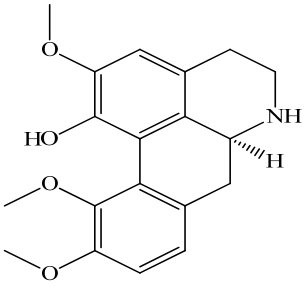
8-oxycoptisine (46)



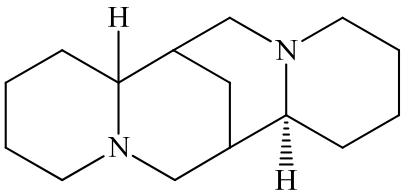
Magnoflorine (47)



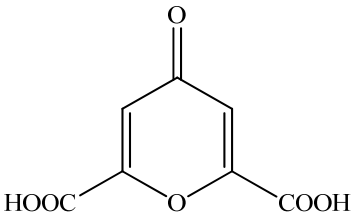
Corydine (48)



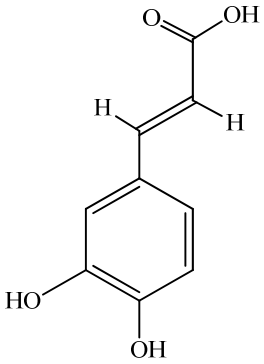
Norcorydine (49)



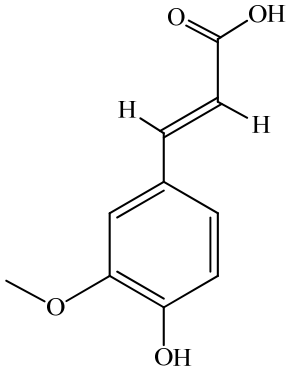
Sparteine (50)



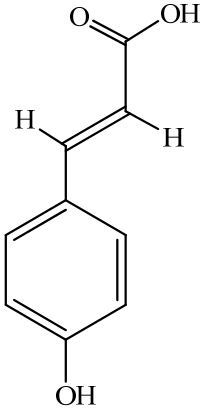
Chelidonic acid (51)



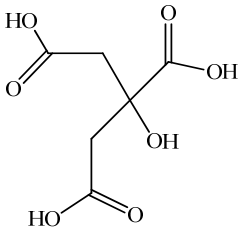
Caffeic acid (52)



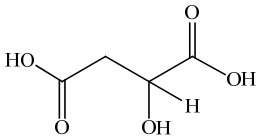
Ferulic acid (53)



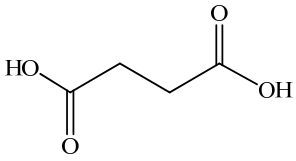
p-coumaric acid (54)



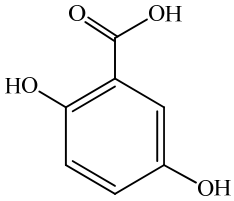
Citric acid (55)



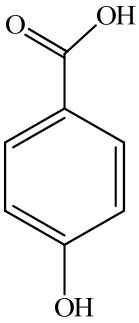
Malic acid (56)



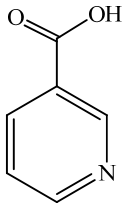
Succinic acid (57)



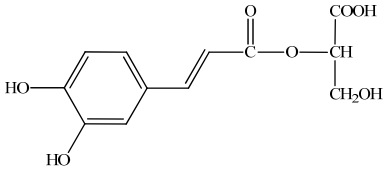
Gentisic acid (58)



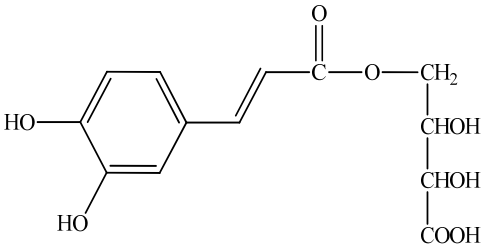
p-hydroxybenzoic acid (59)



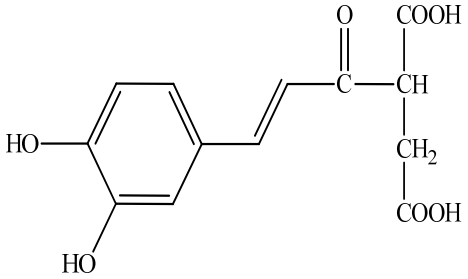
Nicotinic acid (60)



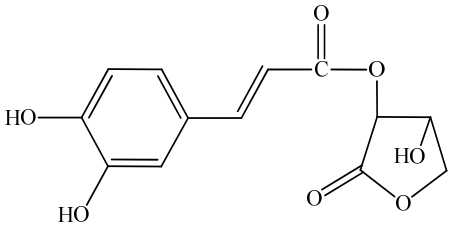
2-(–)-caffeoyl-D-glyceric acid (61)



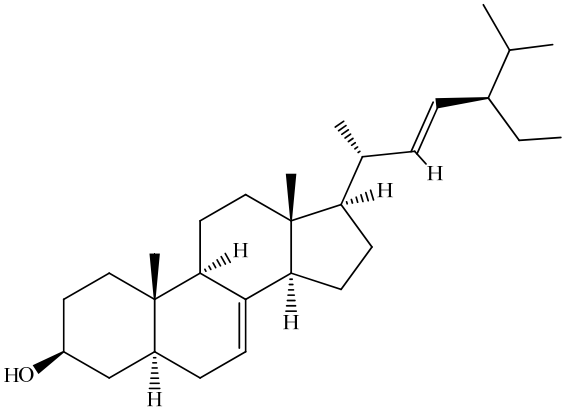
4-(–)-caffeoyl-L-threonic acid (62)



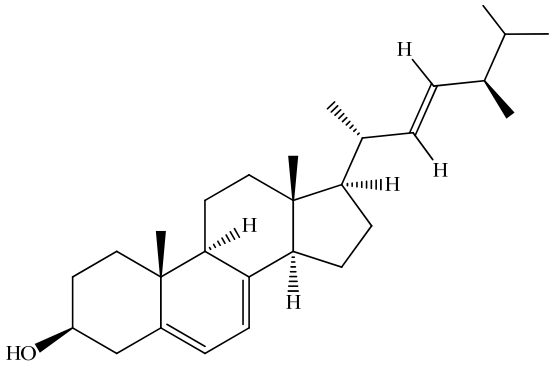
(+)-caffeoyl-L-malic acid (63)



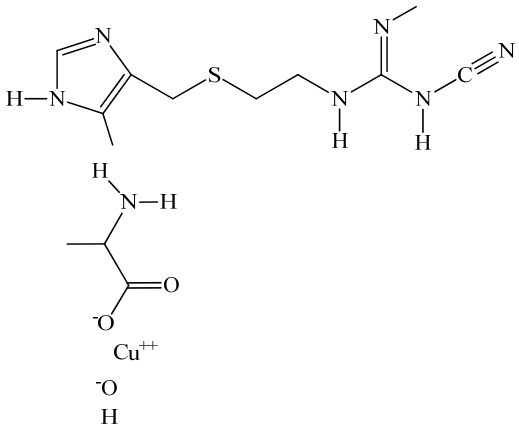
2-(–)-caffeoyl-L-threonic acid lactone (64)



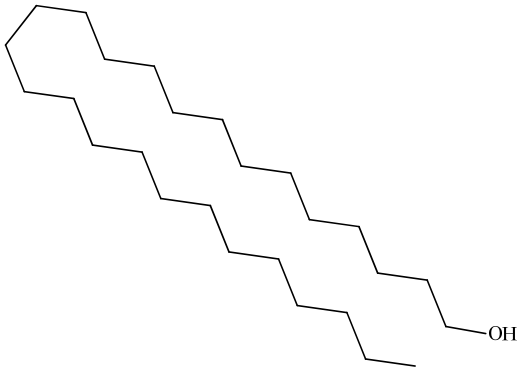
α-spinasterol (65)



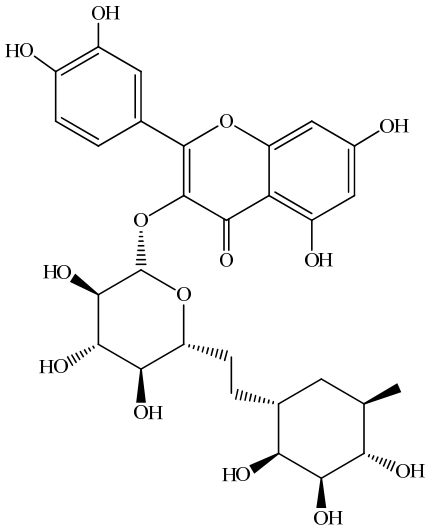
Ergosterol (66)



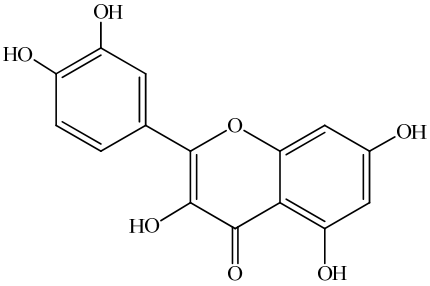
CM-Ala (67)



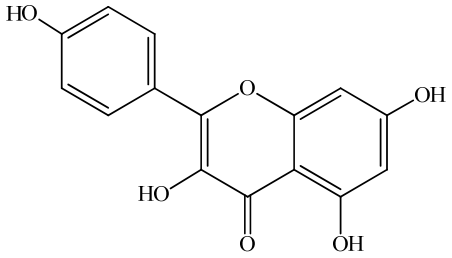
1-hexacosanol (68)



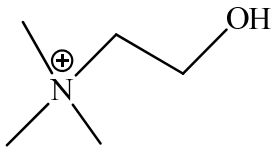
Rutin (69)



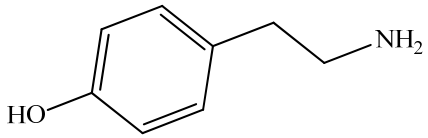
Quercetin (70)



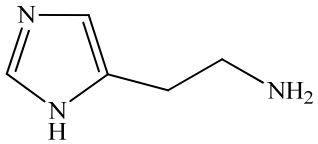
Kaempferol (71)



Choline (72)



Tyramine (73)



Histamine (74)

Fig 1: Chemical structures of *C. majus* constituents.

3. Pharmacological activities

3.1 Antibacterial

C. majus traditionally used as the remedy for toothache. *In vitro* study revealed that the extract of *C. majus* exhibited strong antibacterial activity against *Streptococcus mutans* and the effect of extract was highly related to its chelerythrine content [18]. Kokoska *et al*. reported the antimicrobial activity of the ethanolic root extract of *C. majus* against *Bacillus cereus*, *Candida albicans* and *Salmonella enteritidis* [19]. An immunoactive lectin of *C. majus* was reported to have potent antimicrobial properties against methicillin and vancomycin-resistant Enterococci and Staphylococci [20, 21]. Recent phytochemical analysis of *C. majus* extract led to the isolation of two alkaloidal compounds 8-hydroxydihydrosanguinarine and 8-hydroxydihydrochelerythrine which were found to possess strong antibacterial effect against a methicillin-resistant strain of *Staphylococcus aureus* [22]. Miao *et al*. also reported that sanguinarine and chelerythrine and their derivatives showed potent antibacterial activity against *S. aureus*, *E. coli* and *A. hydrophila* [23].

3.2 Antifungal

The aqueous and methanol extracts of *C. majus* (root and shoot) showed significant inhibitory action against various *Fusarium* strains including *F. culmorum*, *F. graminearum, F. oxysporum* cubense and *F. solani* [24]. Further, bioassay-guided approach led to the isolation of six alkaloidal compounds 8-hydroxydihydrosanguinarine, 8-hydroxydihydrochelerythrine, dihydrosanguinarine, dihydrochelerythrine, sanguinarine and chelerythrine which were reported to show antifungal activity against drug-resistant fungi [25]. The chelerythrine and a mixture of chelerythrine and sanguinarine exerted an antifungal effect against some *Trichophyton* strains, *Microsporum canis*, *Epidermophyton floccosum* and *Aspergillus fumigates* [26]. Recent studies showed that the naturally occurring benzophenanthridine alkaloids (50 mg/ml), sanguinarine and chelerythrine exhibited strong inhibitory action against *Alternaria alternate*, *Curvularia lunata*, *Pyricularia oryza*, *F. solani*, *Valsa mali*, *F. oxysporum* sp. *niveum* and *F. oxysporum* f. sp. *vasinfectum* [27].

3.3 Antiviral

Total alkaloidal extracts of *C. majus* showed antiviral activity against different types of viruses. The ethanol extract of *C. majus* inhibit the growth and development of herpes simplex virus type 1 (HSV-1) [1]. In addition, the crud extract of *C. majus* was found to inhibit HIV-1 and this action was related to its sulphated polyglycosaminoglycan content [28]. *In vitro* study revealed that the benzophenanthridine alkaloidal fractions of different parts showed virucidal activity against HSV-1 and adenovirus type 5 and 12 [29]. The *C. majus* alkaloids such as chelidonine (IC_{50} = 200 µg/ml) and berberine (IC_{50} = 100 µg/ml) were found to have inhibitory action against HIV-I reverse transcriptase enzyme [30].

3.4 Antiprotozoal

Various alkaloids of *C. majus* reported to inhibit the growth of *Trichomonas vaginalis in vitro*. The alkaloid, sanguinarine also caused the protozoa to undergo deformation followed by disintegration [31].

3.5 Anthelmintic

The ethanol extract of *C. majus* whole plant showed considerable anthelmintic activity against *Dactylogyrus intermedius* with an EC_{50} value 71.5 mg/l. Phytochemical analysis revealed that a benzophenanthridine alkaloid, chelidonine was responsible for this activity with an EC_{50} value of 0.48 mg/l [32].

3.6 Antiulcer

C. majus is one of the important constituents of polyherbal formulation, Iberogast® used against irritable bowel syndrome. Pharmacological investigation revealed that the extract of *C. majus* dose dependently produced anti-ulcerogenic effect with reduced acid output and the release of leukotrienes and an increased in mucin secretion and prostaglandin E2 (PGE2) release [33]. Recent findings revealed that purified chelidonic acid from *C. majus* reduced inflammation in mice with ulcerative colitis via inhibiting the production of IL-6, tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2) and hypoxia-inducible factor-1α (HIF-1α) [34].

3.7 Hepatoprotective

C. majus is widely used for the treatment of liver diseases. Several researchers have been established the hepatoprotective effect of the crude extract and its alkaloids. *In vivo* study revealed that the administration of crude extract significantly prevented the carbon tetrachloride induced liver damage and p-dimethylaminoazobenzene (p-DAB) induced hepatocarcinogenesis [35, 36]. The crude *C. majus* extract did not alter the normal liver functions; however it prevented the acetaminophen induced elevation of activated thromboplastin, focal hepatocellular necrosis, plasma enzymes (aspartate

aminotransferase and alanine transaminase) and total bilirubin [37]. The phenolic and alkaloidal fractions of *C. majus* showed choleretic activity by increasing the bile acid flow in rats and human with liver diseases [38]. In addition the nano-formulation of chelidonine was significantly reduced the cadmium chloride induced oxidative stress and hepatotoxicity in mice [39]. Moreover, various high dilutions (potencies) of *C. majus* extract such as Chelidonium-30 (CH-30) and Chelidonium-200 (CH-200) were also reported to ameliorate the liver dysfunctions by reducing the elevated levels of some toxic markers such as acid and alkaline phosphatases, peroxidases, aspartate aminotransferase, alanine transaminase, glutamate oxaloacetate, glutamate pyruvate transaminases, cholesterol and bilirubin in liver of experimental animals [40, 41].

3.8 Hypolipidemic

Recent *in vivo* study showed the hypolipidemic potential of ethanolic *C. majus* extract in rats. Oral administration of the extract (100-300 mg/kg) dose dependently suppressed the serum concentration of triglyceride, low density lipoprotein and high density lipoprotein in hypercholesterolemic rats [42].

3.9 Radioprotective

There was no evidence for the radiation protective effect of *C. majus* extract; however a polysaccharide, CM-Ala, isolated from this plant which considerably reduced the time required for the reconstitution of hematopoietic cells after irradiation treatment [43]. Other studies demonstrated that the ukrain, a semi-synthetic thiophosphoric acid derivative of alkaloid chelidonine, increased survival and enhanced the restoration of hemopoiesis process of irradiated experimental animals [44].

3.10 Antioxidant

In vitro studies demonstrated that the extracts of *C. majus* showed potential antioxidant activity [12]. Phytochemical analysis revealed that the anti-oxidant capacity of *C. majus* extract was greatly depends on its total alkaloid content [45]. *In vitro* study revealed that the oral administration of the polyphenol extracts from different parts of *C. majus* (flowers, leaves, roots, seeds and stems) were found to scavenge various free radicals such as hydroxyl ($HO^{\cdot}$) and peroxyl ($RCOO^{\cdot}$) radicals, hypochlorite (ClO^{-}) and superoxide ($O_2^{\cdot -}$) anions, singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2) [5]. The antioxidative effect of *C. majus* extract was mediated through the activation of transcription factor, FOXO3a followed by the upregulation of major antioxidant enzymes such as catalase and manganese superoxide dismutase (MnSOD) [46].

3.11 Anti-inflammatory and analgesic

Traditionally, *C. majus* is used for the treatment of numerous inflammatory diseases. *In vivo* study demonstrated that the extract of *C. majus* considerably reduced the itching behavior, ear thickness, and the levels of serum IgE, TNF-α and IL-4 in atopic dermatitis mice [47]. Several active compounds have been isolated from this herb such as stylopine, chelidonine, 8-hydroxydihydrosanguinarine, chelerythrine, sanguinarine which showed strong inhibitory actions on LPS-induced production of nitric oxide (NO), PGE2, TNF-α, IL-1β, IL-6 and induction of COX-2 and the expression inducible nitric oxide synthase (iNOS) mRNA in macrophages [48-50]. *In vivo* study showed that sanguinarine, chelerythrine and quaternary benzophenanthridine fraction of *C. majus* significantly reduced carrageenan-induced rat paw oedema and sanguinarine showed higher anti-inflammatory potential than chelerythrine [48]. Recently, the tail-flick studies in mice and rats revealed that the *C. majus* extract (200 mg/kg) and chelidonine (5 mg/kg) showed strong analgesic activity than aspirine [51, 52]. Molecular study revealed that the extract suppressed gamma-aminobutyric acid (GABA) activated ion currents and elevated glutamate-activated ion currents in rat periaqueductal gray (PAG) neurons. These mechanisms were suggested to play important role in the analgesic actions of *C. majus* extract [53, 54].

3.12 Anti-arthritic

The extract of *C. majus* showed potent anti-arthritic activity in collagen-induced arthritis model of mice [55]. Administration of *C. majus* extract (40 and 400 mg/kg) significantly suppressed collagen-induced arthritis which was characterized by decreased production of TNF-α, IL-6, IFN-γ, B cells, γδ T cells, levels of IgG and IgM rheumatoid arthritis factor, and increased proportion of regulatory T cells [55].

3.13 Antialzheimer

Acetylchiocholine is a key factor in the transmission of nerve impulses from one neuron to other in the neuromuscular junction. It is the key hydrolyzing substrate for the enzyme acetylcholinesterase in Alzheimer's disease. The ethanol extract of the aerial parts showed strong acetylcholinesterase (AChE) inhibitory action [3]. Several active alkaloids such as 6-ethoxydihydrochelerythrine, 6-ethoxydihydrosanguinarine, 8-hydroxydihydrochelerythrine, 8-hydroxydihydrosanguinarine, sanguinarine, chelidonine, chelerythrine and berberine have been isolated from the roots and aerial parts of greater celandine. Recent *in vitro* studies showed that 8-hydroxydihydrochelerythrine, 8-hydroxydihydrosanguinarine, sanguinarine, chelerythrine and berberine strongly inhibited the activity of AChE, whereas chelidonine, 6-ethoxydihydrochelerythrine and 6-ethoxydihydrosanguinarine inhibited AChE and butyrylcholinesterase (BuChE) activity [3, 56, 57].

3.14 Immunomodulatory

In the previous section it has been described that the production of inflammatory mediators was inhibited by various constituents of greater celandine. However, the *C. majus* extract reported to improve tonsillar function, cellular and humoral immunity and nonspecific resistance [58]. The extract in combination with recombinant interferon-γ, increased the production of NO and TNF-α in mouse peritoneal macrophages [59]. Recently, a *C. majus* alkaloid, 6-acetonyl-5,6-dihydrosanguinarine, was also found to increase the production of inflammatory cytokines TNF-α, IL-6, and IL-8 in macrophages and dendritic cells [60]. A protein-bound polysaccharide, CM-Ala, has been isolated from the water extract of *C. majus* which was found to increase the production of NO in peritoneal macrophages. CM-Ala was also induced the proliferation of splenocytes and increased the population of granulocyte macrophage-colony forming cells (GM-CFC) [14].

3.15 Natriuretic and antidiuretic

The cadmium is a potent nephrotoxicant and it accumulates and persists in the kidneys. Oral administration of methanol extract of *C. majus* leaves led to restore kidney weight, serum electrolytes, urea and creatinine, urinary excretion of electrolytes and urine volume towards normal values in cadmium-intoxicated rats [61].

3.16 Anticancer

It was determined that the *C. majus* extract suppressed the genotoxic effect of nalidixic acid and furacilin in two different bacterial test systems [62]. The extract of *C. majus* was reported to possess anticancer potentials against variety of chemical carcinogens and inhibited carcinogen-induced angiogenesis and fibroblast proliferation [63]. Several reports demonstrated the anticancer potential of various *C. majus* alkaloids such as chelidonine, sanguinarine, berberine, chelerythrine and coptisine [64, 65]. Chelidonine and sanguinarine induced apoptosis in human lymphoblastic leukaemia cells via caspase 9 and 3 activation and an increase of pro-apoptotic Bax protein [65]. Recently, it was demonstrated that the chelidonine and alkaloidal rich extract (protoberberine and benzophenanthridine) of *C. majus* overcame the multidrug resistance of different cancer cells by apoptosis and cytotoxic effects of chemotherapeutics [66]. Colombo *et al*. reported that the methanol extract of *C. majus* and the coptisine alkaloid showed strong cytotoxicity against human colon carcinoma [67]. However, other constituents including a protein-bound polysaccharide, CM-Ala and lectin isolated from *C. majus* were also suppressed the growth of cancer cells, *in vitro* [14, 21]. The ukrain, a semi-synthetic preparation of chelidonine alkaloid, was demonstrated as a potential anticancer agent against the cancer of lung, pancreas, prostate, breast and urinary bladder [68-72]. Besides, the homeopathic preparations of *C. majus* extract such as CH30 and CH200 showed anti-tumor activity and favorably modulated various toxicity marker enzymes such as acid and alkaline phosphatases, peroxidases, glutamate oxaloacetate and glutamate pyruvate transaminases in liver, kidney and spleen of carcinogen-treated mice [40].

3.17 Antispasmodic

The hydro-alcoholic extract of *C. majus* and its active constituents were found to induce relaxation of acetylcholine and barium-chloride induced contraction of guinea-pig ileums [73, 74]. The alkaloids, chelidonine and protopine at concentrations of $1x10^{-5}$ g/ml organ bath were markedly induced the relaxation (68.8% and 54.8%, respectively) of barium-chloride induced guinea-pig ileums contraction [74]. Another study also revealed the significant contribution of coptisine and (+)-caffeoylmalic acid to the total antispasmodic activity of *C. majus* extract [73]. Besides these pharmacological activities, molecular mechanisms of the major active compounds of *C. majus* on different aspects of the pharmacological actions are summarized in Table 1.

Table 1: Mechanism of actions of major phytochemicals of *C. majus* on different aspects of pharmacology.

Constituents	Biological activity	Mechanism of actions
Chelidonine	Anticancer	Induced apoptosis by up-regulating the expression of apoptotic genes such as p53, Bax, caspase 3 and caspase 8 and the down-regulation of the expression of antiapoptotic genes such as Bcl-2, cyclin D1, protein kinase B, Janus kinase 3, E6 and E7 oncoproteins [66, 75].
	Hepatopretective	Reduced ROS generation, lipid peroxidation and attenuated inflammatory cascade in the liver [39].
	Anti-alzheimer	Inhibited the activity of AChE and BChE [57].
Chelerythrine	Anti-inflammatory	Decreased the synthesis of monocyte chemo-attractant protein 1 (MCP-1), IL-6, TNF-α, PGE2 and NO [76, 77].
	Anti-alzheimer	Inhibited AChE and BChE activity and β-amyloid aggregation [78].
	Anticariogenic	Inhibited cell surface hydrophobicity and adherence by the inhibition of glucosyltransferase and extra-cellular synthesis of water-insoluble glucans [79].
	Nephroprotective	Scavenged free radicals through the inhibition of a PKC pathway and inhibited the production of PGE2 [80].
	Antimycobacterial	Triggered transcriptional changes in the Mycobacterial genome [81].
	Gastroprotective	Inhibited the secretion of inflammatory mediators in gastric mucosa by regulating NF-κB signalling pathway [82].
	Antiplatelet	Inhibited thromboxane formation and phosphoinositides breakdown [83].
	Anticancer	Induced apoptosis via dissipation of mitochondrial membrane potential and activation of caspase 9 and 3 [84].
Dihydrochelerythrine	Antifungal	Inhibited the growth of mycelium and the germination of spores [85].
	Anticancer	Induced apoptosis via dissipation of mitochondrial membrane potential and activation of caspase 9 and 3 [84].
8-hydroxydihydrochelerythrine	Anti-alzheimer	Inhibited the activity of AChE and BChE [3].
6-acetonyl-5,6-dihydrosanguinarine	Immunostimulatory	Increased the production of TNF-α, IL-6, IL-8 and activated NF-κB [60].
Sanguinarine	Antibacterial	Altered membrane permeability and inhibited bacterial DNA synthesis as well as cytokinesis [86, 87].
	Anticancer	Induced apoptosis via activation of caspase 3, 7, 8, and 9, dissipation of mitochondrial membrane potential, increase pro-apoptotic and decrease anti-apoptotic proteins formation [88-90].
	Anti-inflammatory	Decreased the expression of MCP-1, IL-6, TNF-α, and NF-κB genes and increased the expression of IL-1 receptor antagonist [76, 91].
	Antiplatelet	Activated adenylate cyclase, inhibited Ca2+ mobilization, thromboxane B2 production and COX-1 activity [92].
	Immunomodulatory	Inhibited the degranulation and phagocytosis of polymorphonuclear cells (PMN) [93].
	Anti-alzheimer	Inhibited the activity of AChE [56].
Dihydrosanguinarine	Anticancer	Induced apoptosis via activation of caspase 3 and 9, dissipation of mitochondrial membrane potential and the damage of plasma membrane asymmetry [90].
	Antifungal	Inhibited the growth of mycelium and the germination of spores [85].

Constituents	Biological activity	Mechanism of actions
8-hydroxydihydrosanguinarine	Anti-alzheimer	Inhibited the activity of AChE and BChE [3].
Berberine	Antimicrobial	Inhibited DNA and protein biosynthesis in bacteria, fungi and viruses [86].
	Antinephritic	Improved renal hemodynamics by changing prostanoid synthesis [94].
	Anticancer	Inhibited the activity of DNA topoisomerase I, activator protein 1 and COX-2 and inhibited the expression of viral oncoproteins E6 and E7 [95-97].
	Antiangiogenic	Inhibited the expressions proangiogenic factors such as HIF-1α, vascular endothelial growth factor (VEGF), COX-2 and iNOS [98].
	Cardioprotective	Regulated AMP-activated protein kinase activity in heart [99].
	Hypoglycemic	Activated the transport activity of glucose transporter 1 (GLUT1) [100].
	Hepatoprotective	Reduced oxidative stress by scavenging free radicals and inhibited the production of inflammatory mediators in the liver [101].
	Anti-inflammatory	Inhibited the expressions of NO, NF-κB and proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and granulocyte macrophage colony-stimulating factor (GM-CSF) [98].
	Antiviral	Interfered in the viral DNA synthesis [102].
	Anxiolytic	Increased the production of monoamines in the brain and decreased the activity of serotonergic system via activation of somatodendritic 5-HT1A autoreceptors and the inhibition of postsynaptic 5-HT1A and 5-HT2 receptors [103].
	Anti-alzheimer	Inhibited the activity of AChE [56].
Protopine	Antioxidant	Enhanced the activity of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase [104].
	Hepatopretective	Inhibited microsomal lipid peroxidation [105].
	Anti-thrombotic	Inhibited platelet aggregation by inhibiting thromboxane formation, phosphoinositides breakdown and decreased intracellular concentration of Ca2+ [106].
	Analgesic	Inhibited the release of Ca2+ (calcium system) and regulated the opioid and adrenergic systems [107].
	Anti-inflammatory	Inhibited the production of NO, COX-2, PGE2, IL-1β, IL-6, and TNF-α through blocking the activation of NF-κB and phosphorylation of mitogen-activated protein kinase [108].
	Anticancer	Induced apoptosis by increasing cyclin-dependent kinase 1 activity and down-regulating the anti- apoptotic Mcl-1 and Bcl-2 phosphorylation [109].
	Relaxant	Inhibited the intracellular release of Ca2+ [110].
	Anti-alzheimer	Inhibited the activity of AChE [111].
Allocryptopine	Relaxant	Induced relaxation of smooth muscle by inhibiting the activity of phosphodiesterase and elevating the cellular level of cAMP [112].
	Antiarrhythmic	Inhibited the transient outward potassium current [113].
Coptisine	Vasorelaxant	Activated K+ channels and inhibited the extracellular influx of Ca2+ [114].
	Anti-inflammatory	Attenuated the production of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [115].
	Cardioprotective	Inhibited myocardial cells apoptosis via upregulation of Bcl-2 protein, inhibition of caspase-3 activation and Rho/Rho-kinase signalling pathway [115].
	Antinephritic	Improved renal hemodynamics by changing prostanoid synthesis [94].
Chelidonic acid	Anti-inflammatory	Inhibited the production of IL-6, TNF-α, COX-2, PGE2, and HIF-1α and suppressed the activation and expression of caspase1 [34,116].
	Anti-allergic	Inhibited eosinophils and mast cells infiltration and decreased the activity of caspase 1 and the expressions of IL-1β and COX-2 in nasal mucosa [117].
Stylopine	Anti-inflammatory	Inhibited NO, PGE2, TNF-α, IL-1β, and IL-6 production and COX-2 activity [49].
Nitidine	Anti-malarial	Inhibited the formation of β-haematin [118].
	Anticancer	Inhibited the STAT3 signaling pathway and induced cell apoptosis by up-regulating pro-apoptotic proteins (e.g. Bax, cleaved caspase-9 and -3 and cleaved PARP) and down-regulating anti-apoptotic proteins (e.g. Bcl-2 and PARP) [119,120].
	Anti-inflammatory	Inhibited the production of TNF-α, IL-1β and IL-6 via suppressing the phosphorylation of mitogen-activated protein kinases and the activity of NF-κB [121].
	Anticancer	Inhibited STAT3 signaling pathway via preventing STAT3 phosphorylation and its target gene expression [119].
Dihydronitidine	Anticancer	Induced apoptosis via regulating the expression of cyclin-dependent kinase 2 and cyclin E family genes and up-regulating the cell death related genes [122].
Sparteine	Antiarrhythmic	Inhibited Na+ and K+ channels [123].
Angoline	Anticancer	Inhibited STAT3 phosphorylation and its target gene expression [124].

4. Toxicity

C. majus has wide range of clinical applications; however some investigators reported its adverse effects in animals and human. It has been reported that the ingestion *C. majus* latex causes severe irritation of the oral mucosa, throat, stomach, and gut. When the plant is directly applied on skin, it causes irritation, blisters, and allergic contact dermatitis [125]. Recently, there is a controversy between hepatoprotective and hepatotoxic effects of *C. majus*. Several investigators demonstrated the development of liver toxicity after consumption of *C. majus* extract or herbal preparations containing *C. majus* extract [125-127]. *In vitro* study revealed that the alkaloids of *C. majus* such as chelerythrine, sanguinarine, berberine, coptisine, protopine and allocryptopine inhibited liver respiration in mice via inhibition of mitochondrial enzymes such as NADH dehydrogenase and succinate

dehydrogenase [128].

5. Herb-drug interactions

Many people concomitantly use herbal drugs with prescription and non-prescription medications. Herbal drugs and their active compounds were reported to interact with other medications which led to develop serious side effects and/or reduced the efficacy of the medications [129]. Currently there is no information reported on the drug interaction potential of the extract of *C. majus*. However, there were few reports demonstrated the possible drug interaction of the purified active compounds of *C. majus*. Effects of some active constituents of *C. majus* on various drug metabolizing cytochrome P450 (CYP) enzymes are given in Table 2.

Table 2: Inhibition of drug metabolizing CYP enzymes by the alkaloids of *C. majus*.

Active compounds	Drug interactions potential
Sanguinarine	Inhibited the activity of CYP1A1, CYP1A2, CYP3A1, CYP3A4, CYP2C8, CYP2C9, CYP2D1, and CYP2E1 enzymes [130, 131].
Chelerythrine	Inhibited the activity of CYP1A1 enzyme [132].
Chelidonine	Inhibited the activity of CYP3A4 enzyme [66].
Berberine	Inhibited the activity of CYP1A1, CYP1A2, CYP1B1, CYP2D6, CYP2C9, CYP3A4 CYP3A11 and CYP2D22 enzymes [133-135].
Protopine	Inhibited the activity of CYP1A1, CYP1A2, CYP2C19, CYP2B6, CYP2D6 and CYP3A4 enzymes [136].
Allocryptopine	Inhibited the activity of CYP1A2, CYP2B6, CYP2C8, CYP2D6 and CYP3A4 enzymes [136].
Canadine	Inhibited the activity of CYP1A2, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 enzymes [136].
Corydine	Inhibited the activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 enzymes [136].
Stylopine	Inhibited the activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 enzymes [136].

6. Current drugs and future prospect

Since ancient time, the medicinal plants have been considered as the alternative treatments of various diseases and ailments. However, further attention should be required to discover molecular mechanisms behind the therapeutic potential of herbal extracts and their isolated active compounds to promote their commercial uses. Past few decades of pharmacological investigations on *C. majus* extract and its purified bioactive compounds have been shown to possess immense therapeutic potential as antimicrobial, hepatoprotective, anticancer, antioxidant, antialzheimer, immunomodulatory, anti-inflammatory and analgesic agent *in vivo* and *in vitro* studies. Therefore, the pharmacological activities of *C. majus* as well as its purified compounds open up interesting avenues for further research and offer new perspectives in the treatment of these diseases. Different parts of *C. majus* have been used in various polyherbal medicines as well as in combined homeopathic medicines. However, in homeopathic medicine, high-dilutions (potencies) of *C. majus* extract have been also used to treat numerous diseases. Some *C. majus* containing herbal and homeopathic products are already available in the market, including Gastol™ (Ulysses Pharmaceuticals, Kolkata, India) for hyperacidity; Hepeel® (Heel Healthcare, Baden-Baden, Germany) for liver disorders; and Iberogast® (Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) for gastrointestinal disorders [137-138]. Recently, a semisynthetic derivative of *C. majus* alkaloid (chelidonine) known as Ukrain™ (Nowicky Pharma, Vienna, Austria) are commercially available to treat cancer.

The extract of *C. majus* as well as its different purified compounds exhibited a wide range of pharmacological activities such as anti-inflammatory, antimicrobial, anticancer, antioxidant, hepatoprotective, natriuretic and antidiuretic that validate some of the traditional uses of *C. majus*. Immunomodulatory, hypolipidemic and radioprotective potentials of the extract of *C. majus* and its constituents needs to be further evaluated to establish their molecular mechanisms behind such therapeutic properties. The antialzheimer effect of crud extract and its various pure compounds encourage future research for the development of new drug for Alzheimer's disease. Along with various *in vitro* and animal studies, no adequate clinical studies have not been conducted to evaluate its various medicinal effects. Therefore, to justify acclaimed efficacies of *C. majus* and purified compounds against various diseases, well-designed clinical studies are warranted. The hepatoprotective versus hepatotoxic effect of *C. majus* is still a controversial issue; so further toxicological investigations on *C. majus* are further warranted to resolve this issue. Few reports demonstrated the negative interaction between drug metabolizing enzymes and the purified compounds of *C. majus*. However, more details studies are required to evaluate possible herb-drug and herb-herb interaction of *C. majus* including its various purified active compounds. Further studies on the Pharmacokinetics, bioavailability and metabolism of *C. majus* bioactive components in animals as well as in humans are another aspect of future research.

7. Conclusion

C. majus offers a wide range of ethnobotanical and modern utilizations. *In vitro* and *in vivo* studies exhibit numerous therapeutic potential of *C. majus* and its major active compounds with minimal side effects. Though its effect on liver becomes a controversial issue, further studies are required to resolve of this issue. Considering the therapeutic potential of *C. majus* and its use in herbal medicines, it is essential to conduct clinical studies for assessing efficacy and safety of this herb for human uses.

8. Conflicts of Interest

There are no known conflicts of interest associated with this publication.

9. References

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