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ESCHSCHOLZIA CALIFORNICA: A PHYTOCHEMICAL AND PHARMACOLOGICAL - REVIEW

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Abstract:
Phytochemical analysis of Eschscholzia californica showed that both aerial parts and roots contained alkaloids, the latter being richer than the former, it contained up to 1.6% alkaloids. The alkaloids most commonly reported in Eschscholzia californica included sanguinarine, dihydrosanguinarine chelirubine, macarpine, dihydromacarpine, californidine, chelerythrine, dihydrochelerythrine, chelilutine, dihydrochelilutine, sanguirubine, escholtzine, N-methyllaurotetanine, caryachine, O-methylcaryachine, protopine, allocryptopine, reticuline, methyl laurotetanine, hunnemanine, norsanguinarine, pavine alkaloid (6S,12S-neocaryachine-7-O-methyl ether N-metho salt), 1-(3-hydroxy-4-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetra hydroisoquinoline, as well as the dihydro-intermediates. The plant also contained a variety of colours including orange, red and yellow due to its different carotenoid composition. Six flavonol 3-O-glycosides were isolated from the aerial parts of Eschscholtzia californica. *Flavonoids, in the Eschscholzia californica, occurred mainly as quercetin isorhamnetine glycosides. The previous pharmacological studies revealed that the plant possessed antifungal, analgesic, anxiolytic, sedative, behavioural activities and beneficial effect in vasomotor headache with an interesting mechanisms. This review was designed to discuss the chemical constituents and pharmacological effects of Eschscholzia californica.*

Keywords: *Eschscholzia californica, pharmacology, contents, chemicals, therapeutic*

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INTRODUCTION:

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plant derivates had been employed by population to prevent different kind of diseases for centuries. The knowledge of plant properties was acquired by ancient civilization that passed down from generation to generation until today. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-25]. Phytochemical analysis of *Eschscholzia californica* showed that both aerial parts and roots contained alkaloids, the latter being richer than the former, it contained up to 1.6% alkaloids. The alkaloids most commonly reported in *Eschscholzia californica* included sanguinarine, dihydrosanguinarine chelirubine, macarpine, dihydromacarpine, californidine, chelerythrine, dihydrochelerythrine, chelilutine, dihydro chelilutine, sanguirubine, escholtzine, N-methyl laurotetanine, caryachine, O-methylcaryachine, protopine, allocryptopine, reticuline, methyl laurotetanine, hunnemanine, norsanguinarine, pavine alkaloid (6S,12S-neocaryachine-7-O-methyl ether N-metho salt), 1-(3-hydroxy-4-methoxy benzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetra hydroisoquinoline, as well as the dihydro-intermediates. The plant also contained a variety of colours including orange, red and yellow due to its different carotenoid composition. Six flavonol 3-*O*-glycosides were isolated from the aerial parts of *Eschscholtzia californica*. Flavonoids, in the *Eschscholzia californica*, occurred mainly as quercetin isorhamnetine glycosides. The previous pharmacological studies revealed that the plant possessed antifungal, analgesic, anxiolytic, sedative, behavioural activities and beneficial effect in vasomotor headache with an interesting mechanisms. This review will discuss the chemical constituents and pharmacological effects of *Eschscholzia californica*.

Synonyms:

Chelidonium multifidum Moç. & Sessé ex DC., *Chryseis caespitosa* Torr. & A. Gray, *Chryseis californica* (Cham.) Lindl., *Chryseis compacta* Lindl., *Chryseis crocea* Lindl., *Chryseis douglasii* Hook. & Arn. ex Torr. & A.Gray, *Chryseis hypecoides* Torr. & A.Gray, *Chryseis tenuifolia* Torr. & A.Gray, *Eschscholzia absinthiifolia* Greene, *Eschscholzia ambigua* Greene, *Eschscholzia angularis* Greene, *Eschscholzia apiculata* Greene, *Eschscholzia benedicta* Greene, *Eschscholzia bernardina* Greene, *Eschscholzia bernardina var. coarctata* Fedde, *Eschscholzia biolettii* Greene, *Eschscholzia brandegeei* Greene, *Eschscholzia californica var. ambigua* (Greene) Jeps., *Eschscholzia californica var. compacta* (Lindl.) Jeps., *Eschscholzia californica var. crocea* (Benth.) Jeps., *Eschscholzia californica var. douglasii* (Hook. & Arn. ex Torr. & A.Gray) Jeps., *Eschscholzia californica var. luxurians* Fedde, *Eschscholzia californica var. maritima* (Greene) Jeps., *Eschscholzia californica var. peninsularis* (Greene) Munz, *Eschscholzia californica var. stricta* (Greene) Jeps., *Eschscholzia calosperma* Greene, *Eschscholzia chartacea* Fedde, *Eschscholzia clevelandi* Greene, *Eschscholzia cognata* Greene, *Eschscholzia columbiana* Greene,*Eschscholzia compacta* (Lindl.) Walp., *Eschscholzia confinis* Greene, *Eschscholzia crocea* Benth., *Eschscholzia crocea var. sanctarum* (Greene) Fedde, *Eschscholzia cucullata* Greene, *Eschscholzia cyathifera* Greene, *Eschscholzia debilis* Greene, *Eschscholzia diversiloba* Greene, *Eschscholzia douglasii* (Hook. & Arn. ex Torr. & A.Gray) Walp., *Eschscholzia douglasii* Hook. & Arn., *Eschscholzia eastwoodiae* Greene, *Eschscholzia floribunda* Greene, *Eschscholzia floribunda var. gorgonica* Greene, *Eschscholzia floribunda var. gracillima* Fedde, *Eschscholzia foeniculacea* Greene, *Eschscholzia glauca* Greene, *Eschscholzia granulata* Greene, *Eschscholzia granulata var. minuscula* Fedde, *Eschscholzia helleriana* Greene, *Eschscholzia helleriana var. tilingii* Fedde, *Eschscholzia inflata* Greene, *Eschscholzia isostigma* Greene, *Eschscholzia juncea* Greene, *Eschscholzia lacera* Greene, *Eschscholzia leptandra* Greene, *Eschscholzia leptomitra* Greene, *Eschscholzia leucosticte* Greene, *Eschscholzia marcida* Greene, *Eschscholzia marcida var. monticola* Greene, *Eschscholzia maritima* Greene. *Eschscholzia menziesiana* Greene, *Eschscholzia menziesiana var. anemophila* Greene, *Eschscholzia menziesiana var. coarctata* Fedde, *Eschscholzia menziesiana var. nesiaca* Fedde, *Eschscholzia menziesiana var. recedens* Greene, *Eschscholzia microloba* Greene, *Eschscholzia nitrophila* Greene, *Eschscholzia oregana* Greene, *Eschscholzia peninsularis* Greene, *Eschscholzia physodes* Greene, *Eschscholzia picta* Greene,*Eschscholzia pseudoinflata* Fedde, *Eschscholzia recta* Greene, *Eschscholzia revoluta* Greene, *Eschscholzia revoluta var. caudatocalyx* Fedde, *Eschscholzia rigida* Greene,*Eschscholzia robusta* Greene, *Eschscholzia rosea.*, *Eschscholzia sanctarum* Greene, *Eschscholzia scariosa* Greene, *Eschscholzia scariosa var. dichasiophora* Fedde, *Eschscholzia setchellii* Fedde, *Eschscholzia shastensis* Greene, *Eschscholzia straminea* Greene, *Eschscholzia stricta* Greene, *Eschscholzia tenuisecta* Greene, *Eschscholzia thermophila* Greene, *Eschscholzia tristis* Fedde, *Eschscholzia vernalis* Greene, *Eschscholzia xylorrhiza* Greene,

Eschscholzia yainacensis Greene and *Eschscholzia yainacensis var. modocensis* Fedde [26].

Taxonomic classification:
Kingdom: Plantae; **Subkingdom**: Viridiplantae; **Infrakingdom**: Streptophyta ; **Superdivision**: Embryophyta; **Division**: Tracheophyta; **Subdivision**: Spermatophytina; **Class**: Magnoliopsida; **Superorder**: Ranunculanae; **Order**: Ranunculales; **Family**: Papaveraceae; **Genus***:* *Eschscholzia*; **Species**: *Eschscholzia californica* [27].

Common names:
Arabic: Khishkhash California; **Chinese:** hua ling cao; **English:** California-poppy, Golden poppy; **French:** Eschscholzie de Californie, Pavot de Californie; **German:** Kalifornischer Mohn; **Spanish:** Amapolla de California; **Swedish:** Sömntuta [28-29].

Description:
California poppy is a flowering herbaceous annual to deep-rooted perennial. California poppy exhibits a growth form that is low-spreading to erect (0.5 – 2 ft) with basal and cauline foliage which is generally blue-green (glaucous) in appearance. Leaves are ternate, with three finely divided lobes, and are nearly glabrous. Plants produce upright flowers on freely branching stems with four satiny petals, colored bright orange to light yellow; flowers may also have distinct, darker orange centers [30-32].

Traditional uses:
It was used as sedative, analgesic and antispasmodic. It is traditionally indicated for treating the various physical and psychological conditions including insomnia, bedwetting (incontinence), anxiety and nervous tension, particularly in children [28, 33-36]. Indians on the western coast used this herb as a general pain killer, and Indian women would also add this to the food of their (unreactive) mates if pregnancy was desired. Native American used the California Poppy in tea to treat headaches, anxiety, insomnia, as a topical analgesic and to relieve tooth pain. While Native American Indians would cut the root and apply the juice of the Poppy's root to the source of their tooth pain. The plant was also used as a remedy in cases of fever, rapid pulse and spasmodic cough [37].

Chemical constituents:
Both aerial parts and roots contained alkaloids, the latter being richer than the former, it contained up to 1.6% alkaloids. The alkaloids most commonly reported in *Eschscholzia californica* included sanguinarine, dihydrosanguinarine chelirubine, macarpine, dihydromacarpine, californidine, chelerythrine, dihydrochelerythrine, chelilutine, dihydrochelilutine, sanguirubine, escholtzine, N-methyllaurotetanine, caryachine, O-methylcaryachine, protopine, allocryptopine, reticuline, methyl laurotetanine, hunnemanine, norsanguinarine, pavine alkaloid (6S,12S-neocaryachine-7-O-methyl ether N-metho salt), 1-(3-hydroxy-4-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetra hydroisoquinoline, as well as the dihydro-intermediates [38-45].

The amounts of alkaloids isolated from the aerial part of *Eschscholzia californica* were: protopine : 0.514 ± 0.038, californidine: 12.5 ± 1.8, allocryptopine: 0.0120 ± 0.0023, eschscholtzine: 8.700 ± 0.51, sanguinarine: 0.0191 ± 0.0050, chelerythrine: 0.068 ± 0.011, reticuline: 1.095 ± 0.16, n-methyllaurotetanine: 5.68 ± 0.72 and caryachine: 0.410 ± 0.065 mg/ kg dry weight [44].

Eschscholzia californica petals contained a variety of colours including orange, red and yellow due to their different carotenoid composition. Some flowers were white and this has been shown to be due to absence of carotenoids [46].

The carotenoid isolated from *Eschscholzia californica* were included: neoxanthin, violoxanthin, luteoxanthin, auroxanthin, lutein, zeaxanthin, mutatoxanthin, retro-carotene-triol, eschscholtzxanthin, and ζ – carotene [47].

The aqueous ethanolic extract of aerial parts of *Eschscholtzia californica* yielded six flavonol 3-*O*-glycosides. Flavonoids, in the *Eschscholzia californica*, occurred mainly as quercetin isorhamnetine glycosides [48-49].

Pharmacological effects:
Analgesic, sedative and anaxiolytic effects:
The sedative effects of alkaloids detected in *Eschscholzia californica* were attributed to chloride-current modulation, which were widely expressed in the brain mainly at the inhibitory interneurons. Electrophysiological studies on a recombinant ?$_1$?$_2$?$_2$ $GABA_A$ receptor showed no effect of *N*-methyllaurotetanine at concentrations lower than 30 ?M. However, (?)-reticuline behaved as positive allosteric modulator at the ?$_3$, ?$_5$, and ?$_6$ isoforms of $GABA_A$ receptors. The depressant properties of aerial parts of *Eschscholzia californica* were assigned to chloride-current modulation by (?)-reticuline at the ??$_2$?$_2$ and ?$_5$?$_2$?$_2$ $GABA_A$ receptors [44].
The aqueous alcohol extract of *Eschscholzia californica* was evaluated for benzodiazepine, neuroleptic, antidepressant, antihistaminic and analgesic properties. The aqueous alcohol extract of *Eschscholzia californica* induced peripheral

analgesic effects in mice but did not possess antidepressant, neuroleptic or antihistaminic and muscle relaxant effects. Furthermore, the extract did not protect mice against the convulsant effects of pentylenetetrazol. However, the extract showed an affinity for the benzodiazepine receptor, and thus, the sedative and anxiolytic effects of the extract were suppressed by flumazenil, an antagonist of these receptors [35].

A multicenter, double-blind, randomized, placebo-controlled study was carried out in general practice offices in Paris, France and the Paris area. Men and women (N = 264) with mild to moderate generalized anxiety disorder as diagnosed according to the DSMIII- R criteria were participated in the study. Patients received either 2 tablets of placebo or Sympathyl® (Laboratoire Innotech International, Arcueil, France) twice daily for 3 months. Sympathyl contains 75 mg of dry hydroalcoholic extract of the flowering head of hawthorn, 20 mg of dry aqueous extract of California poppy, and 75 mg of elemental magnesium. Efficacy was assessed by change in Hamilton anxiety scale total and somatic scores, change in patient self-assessment, number and percentage of responsive subjects (reduction of at least 50% in Hamilton or self-assessment score) and the physician's clinical global impression. Treatment produced a rapid and progressive fall in anxiety. There was a significant improvement in the total anxiety score (P = 0.005), somatic score (P = 0.054), and self-assessment (P = 0.005) in patients taking Sympathyl for 3 months [36].

Behavioural effects:

The aqueous extract of *Eschscholzia californica* reduced the behavioural parameters measured in a familiar environment test in mice (novelty preference, locomotion and rearings in two compartments test) at doses above 100 mg/kg and in non-familiar environment tests (staircase test) at doses above 200 mg/kg. The aqueous extract of *Eschscholzia californica* at a dose a of 25 mg/kg, also possessed anxiolytic action since it produced an increase of the number of steps climbed by mice in the staircase test (anticonflict effect) and that of the time spent by animals in the lit box when they were confronted with the light/dark choice situation [34].

For the treatment of vasomotor headache:

Because of the effect of *Eschscholzia californica* on endogenous opiates, *Eschscholzia californica* appeared effective in vasomotor headache. However, vasomotor headache has a multifactorial pathogenesis and one factor is anxiety, therefore, therapeutic efficacy of *Eschscholzia californica* in headache could be attributed to its anxiolytic effect [49].

Possible CNS mechanisms:

The herbal drug Phytonoxon N is indicated in nervousness induced insomnia, agitation and/or anxiety. It is composed of alcoholic drug extracts of the plants *Corydalis cava* (20%) and *Eschscholzia californica* (80%). Both plants were rich in isoquinoline alkaloids derived from tyrosine metabolism. Recent research showed that they influence the neurotransmitter activity [33].

A 70% ethanol extract of *Eschscholzia californica* was able to bind to 5-HT_{1A} and 5-HT_7 receptors at 100 mug/ml. The results of radioligand-binding assay of the isolated pure compounds, showed that the activity on the 5-HT_{1A} receptor was at least partly due to the presence of the aporphine alkaloid, which showed the highest inhibition of [3H]8-hydroxy-2-(di-N-propylamino) tetralin ([3H]8-OH-DPAT) binding with an EC_{50} value of 155 nM and a K_i of 85 nM [45].

The protopine was also act as an inhibitor of both serotonin transporter and noradrenaline transporter *in vitro* assays. 5-hydroxy-DL-tryptophan(5-HTP)-induced head twitch response (HTR) and tail suspension test were adopted to study whether protopine has anti-depression effect in mice using reference antidepressant fluoxetine and desipramine as positive controls. In HTR test, protopine at doses of 5, 10, 20 mg/kg dose dependently increase the number of 5-HTP-induced HTR. Protopine at doses of 3.75 mg/kg, 7.5 mg/kg and 30 mg/kg also produced a dose-dependent reduction in immobility in the tail suspension test [50].

The aqueous-alcoholic extract from *Eschscholzia californica* inhibited the enzymatic degradation of catecholamines as well as the synthesis of adrenaline. The extract also dramatically shorten the lag phase in the catalysis of phenolase probably due to their o-diphenol content, furtheremore, dopamine beta-hydroxylase, monoamine oxidase (MAO-B) and diamine oxidases were inhibited by *Eschscholzia californica* extracts. These mechanisms could explain the sedative, antidepressive and hypnotic activities of *Eschscholzia californica* [51].

Protopine, cryptopine and allocryptopine were demonstrated to enhance 3H-gamma-aminobutyric acid (3H-GABA) binding to rat brain synaptic membrane receptors. This effect might be indicate a benzodiazepine-like activity of these alkaloids [52]. (?)-reticuline behaved as positive allosteric modulator at the $?_3$, $?_5$, and $?_6$ isoforms of $GABA_A$ receptors [44].

The roots and aerial parts of *Eschscholzia californica* were extracted with ethanol, column chromatography, preparative TLC, and crystallization. Fourteen isoquinoline alkaloids

were isolated from the ethanolic extract of the roots and aerial parts of *Eschscholzia californica*. All isolated compounds were tested for human blood acetylcholinesterase (HuAChE) and human plasma butyrylcholinesterase (HuBuChE) inhibition activity. None of the compounds isolated significantly inhibited both HuAChE and HuBuChE, but two benzylisoquinoline alkaloids showed inhibitory activity against HuBuChE [40].

The potential effects of ethanolic extracts from *Corydalis cava* and *Eschscholzia californica* on tyrosinase-catalyzed dimerization and/or oxidation of met-enkephalin were investigated. The results showed that the peroxidase-catalyzed dimerization via the tyr-residues is especially inhibited by the *Corydalis cava* extract. However, the tyrosinase-catalyzed reaction yields five different products A-E, according to their HPLC-retention times. Consisting of the 4:1 (v/v) combination of the extracts from *Eschscholzia californica* and *C. cava*, stimulated the formation of minor products A, B and E, whereas the formation of the major products C and D was inhibited. Only products C and D exhibited properties similar to the peroxidase-derived dimer. Product A is likely to be identical to DOPA-enkephalin [53].

Eschscholzia californica effect was evaluated on Tert-Butyl hydroperoxide-induced injury in isolated rat hepatocytes. *Eschscholzia californica* showed both anti-lipoperoxidant and antihepatotoxic activity [54].

Antifungal effects:

The isoquinoline alkaloids, hunnemanine and norsanguinarine isolated from methanolic extract of the whole *Eschscholzia californica*, were checked for their antifungal activity against phytopathogenic fungi, *Alternaria melongenae*, *A. brassicola, A. brassicae, Curvularia lunata, C. maculans, Helminthosporium pennisetti, H. oryzae, H. turcicum, Fusarium undum and F. lini.* Hunnemanine exhibited 100 % inhibition of spore germination of *A. brassicae, H. pennisetti and F. lini* at 1000 ppm whereas norsanguinarine exhibited 100 % inhibition of *A. brassicicola* and *C. maculans* at the same concentration [38].

Metabolism:

The metabolism and the toxicological analysis of the *Eschscholzia californica* alkaloids californine and protopine was studied in rat urine using gas chromatography-mass spectrometry. The identified metabolites indicated that californine was extensively metabolized by N-demethylation and/or single or double demethylenation with consecutive catechol-O-methylation of one of the hydroxy groups. Protopine, however, only underwent extensive demethylenation of the 2,3-methylenedioxy group followed by catechol-O-methylation. All phenolic hydroxy metabolites were found to be partly conjugated. The' systematic toxicological analysis procedure using full-scan gas chromatography-mass spectrometry after acid hydrolysis, liquid-liquid extraction and microwave-assisted acetylation allowed the detection of the main metabolites of californine and protopine in rat urine [55].

Side effects and contraindications:

This plant was considered child safe and based on normal intake levels there were no known side effects from using this herb. The use of the California poppy was not recommended for women who were pregnant or breast-feeding. Users were adviced not to drive or operate heavy machinery after using [28, 56].

It was contra-indicated in glaucoma. It should not be taken with MAOIs, tranquilizers, CNS depressants (e.g. alcohol, opiates, benzodiazepines, anaesthetics, tricyclic anti-depressants, anti-epileptics), and Pentobarbital [57].

CONCLUSION:

This review was design to highlight the chemical constituents and pharmacological effects of *Eschscholzia californica* as a promising plant for many pharmacological purposes as a results of effectiveness and safety.

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