

# Review of Possible Mechanisms of Analgesic Effect of Herbs and Herbal Active Ingredient

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## ABSTRACT

Pain is a distressing feeling caused by damage to different tissues. Consequently the person reacts, and tries to remove the painful stimulus. On the other hand, prostaglandins contribute to the emergence of pain. These compounds are formed and secreted by cyclooxygenase 2 or COX-2 enzymes. It is through inhibiting these enzymes that most of the analgesic medications act. Thus, this study aims to investigate and review some of the scientific findings on analgesic effects and possible active ingredients and analgesic mechanisms of these herbs. **Result:** Nowadays one of the methods to control pain is using non-steroid anti-inflammatory medications. Although the analgesic effects of these medications emerge relatively fast, but their side effects are considered to be a limiting factor in their usage. Therefore researchers are constantly in the search of new medications with less side effects. In recent years the tendency to use herbal medications has significantly increased in the treatment and prediction of these diseases. Since analgesic medications show a wide range of complications therefore using secondary herbal compounds may be an appropriate alternative for chemical medications. In this respect, many

analgesic effects of herbal medications have been brought into attention and it is believed that many natural compounds may serve as new medical compounds. **Conclusion:** Regarding the importance of research about pain and the effort in increasing awareness in this respect and also regarding the problems caused by using opioid medications, it is necessary to find herbal medications.

**Key words:** Analgesic effect, Possible mechanisms, Herbal medications, Herbal active ingredients.

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## INTRODUCTION

Pain emerges when a tissue is damaged. It causes the individual to react and try to get rid of the painful stimulus. It may be stated that pain comprises of three parts: sensory, emotional and affective. Illness, inflammation and damage to the central and the peripheral nervous system leads to significant changes in pain pathways, increase in excitability, and change in gene manifestations, enzymes and receptors.<sup>1</sup> Prostaglandins also contribute to the induction of pain. These compounds have important inter-cell effects and may be released under specific physiological and pathological conditions into the blood flow. Prostaglandins are formed by an enzyme called cyclooxygenase 2 (COX-2). This enzyme is secreted by damaged cells and induces the feeling of pain through connecting to the receptors related to G-proteins and increasing CAMP amount in the cells. As suffering pains causes mental discomfort, humans have always sought a way to remove or decrease pain.<sup>2</sup> Nowadays one of the ways to control pain is using non-steroid anti-inflammatory medications. Although their analgesic effect is induced relatively fast but this side effect is one of their limiting factors in using them. For instance these medications cause stomach dysfunction, dizziness, blurred vision, skin rash, pruritus and liver damage.<sup>1</sup> Furthermore, non-steroid anti-inflammatory medications cost a lot of expense. Therefore researchers are looking for less expensive herbal medications and side less side effects; thus the analgesic effects of many medications have been investigated. Using herbal medications has been popular since antiquity. In the past decade,

there also has been a significant rise in the usage of these medications among people.<sup>3</sup> The increase in the resistance of pathogens toward chemical medications and also their side effects are one of the chief reasons for pharmaceutical companies, doctors and the public to adopt herbal medications for treatment. Therefore secondary ingredients in herbs may serve as good replacements for synthetic drugs. Finding and introducing herbs with medicinal properties such as analgesic properties is necessary and may lay the ground for the treatment of various disorders and complications and opens up new horizons for scientists and researchers.<sup>3</sup> One of the many analgesic ingredients are flavonoids. Flavonoids are polyphenol ingredients that may cross the blood-brain barrier and modulate pain centrally through different mechanisms, such as affecting opioid GABA, alpha 2 adrenergic and inhibiting the enzymes involved in inflammation.<sup>4</sup> Researches also show that flavonoids reduce intercellular calcium through inhibiting the activity of N-methyl-D-aspartate receptors and as a result inhibiting the activity of the enzyme, synthesizing nitric oxide and a2-phospholipase related to calcium and manifest its analgesic properties by decreasing NO and prostaglandins. For instance, flavonoids in tarragon decrease pain through their protective properties operating against oxidative stress caused by hyperglycemia and ingredients with similar properties to benzodiazepines.<sup>5</sup> Regarding the importance of research about pain and the effort in raising awareness in this respect and also regarding the problems caused by using opioid medications, it

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is necessary to try to find herbal medications. Thus, this study aims to investigate and review some of the scientific findings on analgesic effects and probable active ingredients and possible analgesic effect mechanisms of these herbs.

## METHODS

For this review, we used a diversity of sources by searching through PubMed/Medline, Scopus, Web of sciences, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents: analgesic effect, possible mechanisms, herbal medications, herbal active ingredients.

## RESULT

Analgesic effects of Medicinal plants and their active ingredients

Medicinal plants induce a biological equilibrium due to their natural active ingredients and their concomitance with other ingredients and prevent accumulation of medical substances in the body. Some of these abundant ingredients in herbs with analgesic properties are flavonoids. Flavonoids prevent the inducement of prostaglandins through inhibiting cyclooxygenase in the inflamed tissue.<sup>5</sup> Flavonoids such as apigenin, reduce the accumulation of flowing lipids necessary for signaling pain. Therefore, flavonoids reduce inflammatory pain through inhibiting the receptors and the signaling cascade.<sup>5</sup> From the many of the analgesic herbal ingredients, menthone, tannin and menthol may be mentioned. Studies show menthol has an exclusive receptor in the cell membrane which causes the resting flow toward the cell to reduce. It also increases the cellular stimulation threshold. This ingredient through affecting calcium channels in the nervous cell membranes, especially pain pathway neurons, reduces the inward calcium flow and reduces synaptic transmission and induces pain.<sup>6</sup> In (Table 1) some of the most important herbs with analgesic properties have been mentioned along with their

possible mechanisms. Herbal active ingredients reducing pain include flavonoids (Quercetin), volatile oils (monoterpenes and sesquiterpene). Phenol ingredients such as Thymol and Carvacrol, Coumarin, glycoside steroids, alkaloid ingredients, organic acids, tannins, Limonenes, Cineols and Saponins.<sup>3</sup>

The presence of flavonoid and iridoid compounds in siderites extract is responsible for analgesic effects and is the reason for its traditional use. Linalool is also one of the monoterpene ingredients in cinnamon that affect pain receptors and induce an analgesic effect. Phenols such as eugenol inhibit calcium from entering the cell and thus relieve pain.<sup>7</sup> Gingerol, an active ingredient in rhizome ginger, has a strong ability in inhibiting prostaglandins. And through mechanisms that reduce vascular permeability and production of pain mediators, is the chief analgesic agent of ginger.<sup>3</sup> Analgesic effect of *ziziphora clinopodioiedes* from the Lamiaceae family has been attributed to pulegone that seems to do this through inhibiting acid arachidonic and prostaglandins synthesis and affecting opioids.<sup>1</sup>

## DISCUSSION

### *Glycyrrhiza glabra*

*Glycyrrhiza glabra* root (rhizome) includes glycerin which is 50 times more than sucrose. Its commercial extracts include glycyrrhizin in ammonium salt and *G. glabra* alcoholic extract which comprises of four active ingredients: glycaemia coumarin glycerin, hydro glia aspirin C and dehydrogol aspirin D. Other ingredients of this herb are flavonoids including Isoflavone, Liquiritin, iso liquiritin, formononetin, poly saccharides, esterole, coumarines, asparagine, amino acids, resin, starch, oil essences, and saponins.<sup>8</sup> This herb is a remedy for coughing, it has mucolytic, anti-inflammatory and laxative properties and is used effectively to treat stomach and duodenum illnesses.<sup>9</sup> It is also used in treating upper respiratory tract infections, bronchitis, peptic ulcers, duodenal ulcers, chronic gastritis, rheumatism, arthritis, and adrenal

**Table 1: Some of the medicinal plants with analgesic effects and their possible analgesic mechanisms**

Number	English name	Scientific name	Possible mechanism	Reference
1	Salvia hydrangea	<i>Salvia hydrangea</i>	Inhibiting prostaglandins synthetic pathways	(10)
2	Lavender	<i>Lavandula officinalis</i>	Affecting inflammatory processes	(11)
3	Lemon balm	<i>Melissa officinalis</i>	Central analgesic mechanism	(12)
4	Pennyroyal	<i>Mentha pulegium</i>	Inhibiting NO synthesis and inflammatory mediators and NMDA receptors and stimulating opioid receptors	(13)
5	Wall thyme	<i>Ziziphora tenuior</i>	Inhibiting the release of acid arachidonic and the synthesis of prostaglandins and affecting the opioid system	(14)
6	Wall Germander	<i>Teucrium polium</i>	Connecting to pain receptors and affecting channels sensitive to ligand and decreasing sodium entrance rate	(15)
7	Betony	<i>Stachys lavandulifolia</i>	Inhibiting cyclooxygenase	(16)
8	Celery	<i>Apium graveolens</i>	Inhibiting cyclooxygenase	(1)
9	Aucheri	<i>Dorema aucheri</i>	Inhibiting NO synthesis and NMDA receptors and stimulating opioid and adrenergic systems	(17)
10	Liquorice	<i>Glycyrrhiza glabra</i>	Inhibiting leukocyte extravasation and producing inflammatory mediators in neutrophils	(18)
11	Saffron	<i>Crocus sativus</i>	Possibly inhibiting NMDA receptors and synthesizing nitric acid	(19)
12	Fennel	<i>Foeniculum vulgare</i>	Serotonergic and histaminergic receptor	(20)
13	St Johns wort	<i>Hypericum perforatum</i>	Inhibiting COX and LO-5 enzymes	(21)

glands failure. Its products are widely used in pharmaceuticals as sweetener and as binder. Liquorice is useful in treating skin complications such as dermatitis, eczema and pruritus. It has anti-infectious, anti-septic, anti-bacterial, anti-hepatotoxicity, anti-virus and antiphlogistic characteristics. Liquorice causes antispasmodic effects in gastrointestinal tract and visceral pain relief through inhibiting phosphodiesterase 3. Its hydroalcoholic extract, through increasing defensive factors of gastric mucosa induces anti-ulcer mechanisms.<sup>8,9</sup> Glycyrrhizin is another one of the liquorice ingredients. Its oral use inhibits 11- $\beta$  dehydrogenase enzyme and consequently increases the blood cortisol level. It is probable that this ingredient reduces pain through reducing inflammation.<sup>9</sup>

#### *Melissa officinalis*

Shoots contain great concentrations of its essence. The most important ingredients of *Melissa officinalis* essence are citronella, citral, geraniol, ocimene, limonene, caryophyllene, linalool and other ingredients such as tannin, flavonoid and polyphenol. Its leaves contain aldehyde monoterpene, flavonoids (quercetin, luteolin), polyphenolic ingredients (rosmarinic acid, caffeic acid) and triterpenes. It also contains sesquiterpene and ingredients containing oxygen.<sup>22,23</sup> *M. officinalis* is sedative, cardiactonic, memory and mental tonic. This herb is used for treating gastrointestinal, cardiovascular and neural illnesses and its ointment is antiherpes. It is also used for treating insomnia, sleeping disorders, anxiety, depression, neural illnesses, migraine, nausea, nervous stomach, anorexia, colic, cough, irregular menstruation, toothache and nervous tremors. Its lotion, obtained through brewing its herb, relieves pain if applied to scars and wounds.<sup>26</sup> One of its most important analgesic effects has been attributed to limonene. Through reviewing the past studies on herbal extracts with analgesic effects, it may be concluded that it is probably limonene that is responsible for the analgesic and anti-inflammatory properties of dracocephalum. This ingredient is present in celery essence, comprising more than 60 percent and in *Anethum graveolens* comprising about 32 percent of its volume.<sup>3</sup>

#### *Anethum graveolens*

The most important active ingredient in *Anethum graveolens* is d-carvone which is present in both its herb and its seed. Its fruit (seed) contains 102 to 7-7 percent essence, dylanoside (a xanthone glycoside), coumarin, kaempferol, vicenin, myristicin and other flavonoids, phenol acids, protein and fat. The main flavonol glycoside in its leaves are quercetin, quercetin 3- $\beta$ -D-glucuronide and isorhamnetin 3- $\beta$ -D-glucuronide.<sup>24</sup> This herb is used in traditional medicine as a body and stomach tonic, digestive, carminative, anti-convulsant, antiemetic and sedative. It is used to increase the secretion of mother's milk. *A. graveolens* has a plethora of biological benefits. It has appetizing, carminative, diuretic, anti-spasm, anti-jaundice, anti-cholesterol, anti-cancer and anti-oxidation properties. It reduces LDL and tri-glyceride and increases HDL. Limonene ingredients, carvone and kaempferol in dill have analgesic and anti-inflammatory effects. Analgesic effects of carvone are achieved through affecting glutamate receptors, furthermore its analgesic activity may be through decreasing the neuropathy of the peripheral nerves. Kaempferol also has analgesic and anti-inflammatory effects. It acts by inhibiting cyclooxygenase 2 enzymes through suppressing SRC kinase. Limonene suppresses the activity of prostaglandins through inhibiting cyclooxygenase 1 and 2 enzymes and thus is effective in inhibiting pain and inflammation.<sup>25,26</sup>

#### *Matricaria recutita*

The essence in *Matricaria recutita* blossoms includes Proazulenes, farnesene, alfa bisabolol, bisabolol oxide, spiroether, and flavonoids such as: anthemidin, luteolin, tannin, rutin and bitter glucosides, coumarines, mucilage substances and pectin compounds.<sup>27</sup> This herb is used to decrease fever and sweating, relieving headache and migraine pains and

arthrosis, menstrual period disorders and menopause, reducing blood pressure and relieving spinal column complications. It is anti-infection, stomach anti-inflammation, appetizer and carminative. It is used in treating rhinorrhea and agitation. It is also used to treat hemorrhoid, eliminate wrinkles around eyes, moisturize skin and make hair shiny.<sup>27</sup> *M. recutita* blossom contains some compounds like benzodiazepines and is proved to have analgesic properties. Researches have proved that the simultaneous injection of compounds present in chamomile blossom like flavonoid quercetin increases the tolerance to the analgesic effects of morphine. It also has been shown that flavonoid compounds of *M. recutita* blossoms act as CNS activator molecules. And have introduced the flavonoid chrysenes, as a partial agonist to benzodiazepine receptors. So far *M. recutita* blossoms has been used in treating skin inflammation, hemorrhoid, foot scars, urine burns in infants and in relieving pain and increasing the recovery rate of damaged tissues.<sup>28,29</sup>

#### *Lavandula officinalis*

The essence in *Lavandula officinalis* shoots contains flavonoid, tannin and coumarine. Its essence contains more than 40 compounds, the most important ones being linalool, linalyl acetate, cineol, nerol and borneol. Its other medical compounds are geraniol, alpha pinon, camphor, acid butyric, valeric acid, ursolic acid and luteolin flavonoids. *L. officinalis* root is a strong anticonvulsant and its leaves and blossoms are used to relieve pain. The essence of this herb has tranquilizing and anti-depression properties. It is also used for removing helminth, opening congestions, memory tonic, gout relief and rheumatism and also for relieving skin diseases such as eczema, acne, and burns and as a burn relief and insect sting relief.<sup>30</sup> Linalool and linalyl acetate in *L. officinalis* shoots able to stimulate parasympathetic nervous system, and is efficient on relieving the pain following laparoscopic surgery. 1, 8 cineol are the most important active ingredient of this herb with analgesic properties. This ingredient may prevent the formation of prostaglandins such as PGE2 and leukotrienes such as LtB4, which are pain mediators, through inhibiting acid arachidonic metabolism. In clinical researches it has been proved that *L. officinalis* shoots essence may prevent the degranulation of host cells and the releasing of histamines. Ketones in lavender may efficiently reduce inflammation and improve sleeping.<sup>31</sup>

## CONCLUSION

Medicinal plants may establish a biological equilibrium and prevent the accumulation of medical ingredients due to their active ingredients. Having low complications or not having it at all, is their considerable advantage over the chemical medications. The most important herbal ingredients with analgesic effect include flavonoids, volatile oils. Phenol compounds, alkaloid compounds, organic acids and essence. These compounds prevent the formation of cyclooxygenase enzyme and consequently prevent the formation of prostaglandins. Regarding the priority of pain relief for patients, it is necessary to increase the awareness in order to deal with harmful bodily and mental effects of pain. And one of the possible solutions for obtaining analgesic medications is further investigating medical herbs and natural compounds.

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