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Review on antispasmodic activity of *crocus sativus* and *abies*

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Abstract
Antispasmodic activity is used to relieve spasm in smooth muscle. *Crocus sativus* commonly known as saffron belong to iridaceae family, rich in carotenoid used in traditional medicine such as cough, stomach disorders, amenorrhea and asthma. The relaxant effect of *crocus sativus* on smooth muscle are due to its constituents such as safranal, crocin, crocetin and kaempferol. The therapeutic effects of this plant are also suggested in blood vessels and various smooth muscles. It is used in siddha formulation such as kungamapoo tablet *Abies webbiana* belong to pinaceae family rich in flavonoids and tannin used for anti-spasmodic, bronchodilator. They show ca++ channel blocking effect. It is main ingredient in siddha formulation such as thalisathichooranam, elathychooranam and thalisathivadagam. In this study, we have investigated antispasmodic activity of *Abies webbiana* and *crocus sativus*.

Keywords: crocus sativus, antispasmodic activity, *Abies* webbiana, phytochemicals

Introduction
The antispasmodic effect of drugs is commonly used for the reduction of excessive smooth muscle contractility which is responsible for cramping and discomfort in smooth muscle that includes abdominal area and blood vessels. Irritable bowel syndrome, colitis, pancreatitis, gastritis, gall stones, dysmenorrheal cases may require antispasmodic treatment. Siddha system of medicine is a distinct therapeutic science with many single drugs and compound formulation used for treating a broad spectrum of ailments. The drug sources are obtained from plant, mineral, metal and animals. Herbal drugs have been used widely in many countries because of its availability, cost efficient and safer than the synthetic drugs.
Several aromatic plants were used in traditional medicine for the treatment of spasm. Nowadays, antispasmodic botanical remedies are used by constantly increasing number of patients for symptomatic treatments of dyspepsia, colonic or ureteral spasms and uterine craps. Hence this review aimed at the investigation of antispasmodic effect of two plants namely *crocus sativus* and *abies webbiana* belong to Iridaceae and Pinaceae respectively.

Methods
A study was performed in PubMed, Research gate, Ncbi, Scholarly articles. The search terms "Antispasmodic activity" (spasmolytic) *crocus sativus* and *abies webbiana* were used for data selecting only articles on antispasmodic activity of *crocus sativus* and *abies webbiana* were focused.

Phytochemical Analysis
Crocus Sativus
Tamil Name: Kungumapoo
Parts used: Stigma

Scientific Classification
Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Asparagales
Family: Iridaceae
Genus: Crocus
Species: *C. sativus*

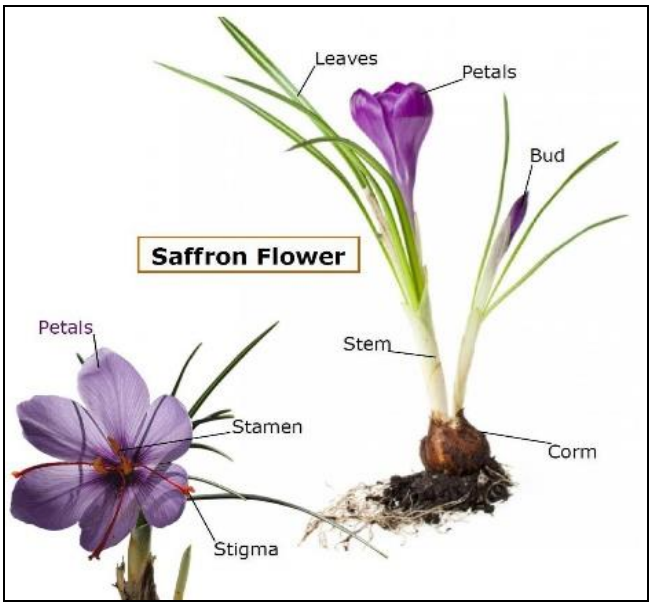

Fig 1

Action

- Stimulant
- Stomachic
- Anodyne
- Antispasmodic

Phytochemical Consituents

- Crocin
- Crocetin
- Picrocrocin
- Carotene
- Lycopene

Mechanism of Action

Crocus sativus commonly known as saffron is a small perennial plant belong to Iridaceae family. It has gray green hairy margins leaves and grows to about 30-35 cm long and funnel shaped reddish-purple flower with red stigmas. The stigma is commonly used as a flavoring and yellow coloring addictive in foods.

Main constituents of saffron stigma are crocin (responsible for colour), picrocrocin (responsible for bitter taste) and safranal(responsible for odour and aroma). It contains more than 150 volatile aroma yielding compounds and non -volatile compounds which are carotenoids including zeaxanthin, lucopene, alpha and beta carotene. *C.sativus* has been used as antispasmodic, eupeptic, gingival sedative, carminative, expectorant, stimulant, stomachic, aphrodiasic and emmenagogue medicine.

The aqueous extract of saffron stigma, safranal and crocin decreased mean arterial blood pressure in a dose-dependent manner. The hypotensive effect of the extract is perhaps due to its relaxant effect on vascular smooth muscle. The results also suggested that safranal, the major constituent of the plant, contributes to the hypotensive activity. Safranal also showed concentration-dependent relaxant effect on tracheal smooth muscle.

Effects of *C.sativus* on different types of smooth muscles:

- AE of saffron stigma decreases the mean arterial blood pressure of animals and reduces the enhanced mean systolic pressure.
- AE and EE have inhibitory effect on heart rate and contractility and have potential relaxing effect on tracheal smooth muscle.
- AE and EE of *C.sativus* petals reduces the blood pressure
- AE of safranal and saffron has antitussive effect.
- Safftron has relaxant effect in uterine contraction.
- Safranal has relaxant effect on tracheal smooth muscle.

Calcium Channel Antagonistic Effects

Crocin could inhibit Ca^{2+} influx and release of intracellular Ca^{2+} which stores in the endoplasmic reticulum in bovine aortic smooth muscle cells. It was also shown that reduction of intracellular Ca^{2+} release may contribute to relaxation of the corpus cavernosum, leading to erection. Coronary and other diseases in cardiac or brain blood vessels are considered to be due to the excessive influx of Ca^{2+} into cytoplasm. So, Ca^{2+} channels blockers are of therapeutic value in treatment of these diseases. The effect of *C. sativus* on Ca^{2+} influx in isolated rat

aortas was investigated using 45Ca as a radioactive tracer, and their calcium antagonistic effects were evaluated. Ca^{2+} uptake in isolated rat aorta rings in normal physiological status was not markedly altered by these drugs, whereas Ca^{2+} influx induced by norepinephrine 1.2 µmol/L and KCl 100 mmol/L were significantly inhibited by *C. sativus* in a concentration-dependent manner.

The results showed that Ca^{2+} influx through receptor-operated Ca^{2+} channels and potential-dependent Ca^{2+} channels can be blocked by the plant. It is conceivable that the hypotensive effect of saffron in chronic treatment is related to its inhibitory effect on smooth muscles via blocking calcium channel or inhibiting sarcoplasmic reticulum Ca^{2+} release into the cytosol.

Crocin also concentration-dependently inhibited the total cholesterol (TC) and Cholesteryl ester (CE) elevation induced by Ox-LDL. The results indicated that crocin could inhibit the increased intracellular [Ca^{2+}] in smooth muscle cell.

Kungumapoo mathirai is the drug which is used to treat various diseases such as sinusitis, gastritis, chronic constipation and hyperhidrosis in Siddha medicine. The dosage of the drug is 1-2 tablets in the morning and evening after food with the adjuvants like honey, or with mother's milk in case of children. The preparation of this drug is to take all the below mentioned drug in equal ratio and make it fine. Then the powdered medicine should be churned with the decoction made by the saffron for 3 hours continuous.Then make the churned medicine into small pills with weight of 50mg each. Most of the drugs included in the preparation of Kungumapoo Mathirai have anti-cholinergic effect or antispasmodic effect. In Siddha system of medicine Kungumapoo Mathirai has the effect of anti-cholinergic or antispasmodic effect. The ingredients of Kungumapoo mathirai are

- Kunguma poo (*Crocus sativus*)
- Sukku (*Zingiber officinalis*)
- Venmilagu (*Piper nigrum*)
- Vaal milagu (*Piper cubeba*)
- Koshtam (*Costus speciosus*)
- Omam (*Carum capticum*)
- Thippili (*Piper longum*)
- Lavangam (*Syzygium aromaticum)*
- Elarisi (*Elettaria cardomom*)
- Korosanam (Ox bile)
- Vengaram (Sodium biborate)
- Lingam (Red Sulphide of Mercury)
- Sambarani poo (*Styrax benzoin*)

Fig 2

All the herbs used in this formulation has the action of widening the bronchial passages so it is proven that all these ingredients can cure the diseases of respiratory passage through its antispasmodic activity.

Abies Webbiana
Tamil Name: Thalisadhi
Parts used: Leaves

Scientific Classification
Kingdom: Plantae
Division: Pinophyta
Class: Pinopsida
Order: Pinales
Family: Pinaceae
Genus: Abies
Species: *A.webbiana*

Action
- Stomachic
- Carminative
- Expectorant
- Tonic

Phytochemical Consituents
- Taxol
- Taxine
- Taxinine
- Ephedrine

Mechanism of Action
Abies webbiana commonly known as thalisapatri belong to the Pivaceae family grown in northern India. It is a large tree grows up to 50m height. It acts as an expectorant, carminative, stomatic. The phytochemicals include steroids, terpenes, sugar, phenol, flavonoids, tannins, saponins and quinones.
Smooth muscles are a key element present in the internal structure of multiple abdominal organs including stomach, intestine, bladder or uterus, receiving innervation from the autonomic nervous system but also autocrine or paracrine stimuli. Recently, considerable progress was made to understand in great molecular detail the complex physiology of smooth muscle contraction. Excitation-contraction coupling occurs when Ca^{2+} ions enter from the extracellular side into the smooth muscle cells through sarcolemma voltage-dependent calcium channels, being also released from intracellular stores via inositol 1,4,5-triphosphate receptor (IP3R) situated on endoplasmic reticulum (ER). The calcium release from ER is triggered by the binding of agonists like acetylcholine or histamine on specific G-protein coupled receptors (GPCRs) from the membrane of smooth muscle cells, which activate phospholipase-C (PLC) to generate IP3. After the intracellular concentration of calcium has increased, Ca^{2+}ions bind to calmodulin (CaM) and phosphorylate the myosin light-chain kinase (MLCK) with the subsequent activation of the contractile apparatus.
Thus, the identification and characterization of multiple molecular targets involved in smooth muscle contraction has led to the development of a variety of drugs able to reduce excessive contractility responsible for cramps and colics of the abdominal organs. Among potential new drug candidates, sterols have become increasingly attractive due to their complex chemical composition and multiple pharmacological mechanisms such as inhibition of voltage-dependent calcium channels, modulation of potassium channels, antagonism of cholinergic receptors, and modulation of intracellular cyclic adenosine monophosphate (cAMP).
The opening of voltage-dependent calcium channels (VDCCs) is directly responsible for Ca^{2+}influx into the smooth muscle cells, partially triggering the contractile mechanism. Thus, inhibition of VDCCs has a good potential of relaxing smooth muscles, already used by several antispasmodic drugs like pinaverium. Sterols have been studied for their antispasmodic effect, the inhibitory effect on voltage-dependent calcium channels being the most commonly reported mechanism of action.
The main intracellular second messengers cAMP and cGMP are directly involved in smooth muscle relaxation. cAMP is generated by adenylyl cyclase mainly as a result of beta-adrenergic receptor activation. cGMP is produced by soluble guanylyl cyclase activated by nitric oxide or other mediators. Both cAMP and cGMP activate protein kinases PKA and PKG which may relax smooth muscles either by increasing the expulsion of calcium from the cell or by activation of MLC phosphatase which inhibits MLCK. The levels of cAMP and cGMP are severely reduced by the intervention of phosphodiesterase (PDE) involved in their degradation to inactive metabolites.
In Siddha medicine Thalisathi choornam used in treatment of gunmam(peptic ulcer), kaamalai(jaundice), suram(fever), velai(leucorrhea), irumal(cough), Sali(phlegmatic conditions/pneumonia), a wide range of kaba noigal and kaadhu noigal(ear disesases). The dosage of the drug is 1 gram in honey. The ingredients of Thalisathi chooranam are
- Thaaleesapathiri (*Taxus beccata*)
- Lavangapattai (*Cinnamomoum zeylanicum)*
- Elakkai (*Eletteria cardamomum*)
- Chukku (*Zingifer officinale*)
- Adhimadhuram (*Glycyrrhiza glabra*)
- Perungayam (*Ferula asafetida*)
- Nellimulli (*Emblica officinalis*)

- Kostham (*Saussurealappa*)
- Thippili *(Piper longum*)
- Seeragam (*Cuminum cyminum*)
- Sadakuppai (*Anethum sowa*)
- Karunseegram (*Nigella sativa*)
- Thippilimoolam (*Piper longum*)
- Lavangam *(Syzygiumaromaticium*)
- Millaku (*Piper nigrum*)
- Jaadhikai (*Myristica fragrans*)
- Sadaamanjil (*Nardostachys jatamansi*)
- Sirunaga poo (*Cinnamomom verum*)
- Shenbagamokku (*Michelia champaca*)
- Vaividangam (*Embelia ribes*)
- Omam (*Trachyspermum ammi*)
- Kothamalli (*Coriandrum sativum*)
- Thandrikai (*Terminalia bellarica*)
- Sugar (*Saccharum officinuram*)

Conclusion

This review shows the antispasmodic activity of two plants *abies webbiana* and *crocus sativus*. The main mechanism of antispasmodic effect was represented by inhibition of calcium channels, modulation of potassium channels and modulation of intracellular CAMP. These plants also have other therapeutic effects but need future clinical studies.

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