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PHARMACOLOGICAL REVIEW ON *PHYSALIS* SPECIES: A POTENTIAL HERBAL CURE – ALL

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ABSTRACT

In recent times, focus on plant research increased all over the world. *Physalis* species plants are widely distributed all over the India, china and other sub tropical countries. Alkaloids, Flavonoids and withanolides are the primary constituents of *Physalis* species mainly believed to be responsible for its wide therapeutic actions. Apart from the Analgesic activity, these plants are used to treat Cancer, Leukemia, Hepatitis, having properties like hepatoprotective, Diuretic, Anti Ulcer, Anti Microbial, Anti Oxidant, Anti inflammatory, Renal protective activity. The present review attempts to provide comprehensive information about different *Physalis* species their chemical constituents, Pharmacology , mechanism of action, various preclinical current research prospects of the herbs are discussed.

KEYWORDS: Physalis species, chemical constituents, Alkaloids, Flavonoids.

INTRODUCTION

Plants have been used as treatment for thousands of years, based on experience and folk remedies and continue to draw wide attention for their role in the treatment of mild and chronic diseases. In recent times, focus on plant research has increased all over the world and a large body of evidence has been accumulated to highlight the immense potential of medicinal plants used in various traditional systems of medicine. Specifically Physalis species plants have very important medicinal herb used in the orient, which are becoming popular all over the world. In this article we are going to discuss about different plants belonging to Physalis species they are *Physalis peruviana, Physalis angulata, Physalis alkekengi, Physalis ixocarpa, Physalis pruinosa, Physalis floridana, Physalis minima.*

Commonly known as Cape gooseberry, wild gooseberry, chainese lantern, Mexican husk tomato, wild cherry, Husk tomato, Wild Cape gooseberry respectively it has been used as a medicine in the ayurvedic tradition these plants are widely distributed all over India, china, other western countries these are having the therapeutic effects like Analgesic activity, these plants are used to treat Cancer,[1] Leukemia, Hepatitis, having properties like hepatoprotective, Diuretic, Anti Ulcer, Anti Microbial, Anti Oxidant, Anti inflammatory, Renal protective activity .Despite large number of studies reported over the past decades on the evaluation of biologically active components and their mechanism of action , the outcome of these studies is still unsatisfactory. Although there have been several claims regarding the underlying mechanism involved in the biological action of this herb, more scientific data are needed to justify its ever increasing use. Therapeutic potential of these plants in terms of its efficacy and versatility is such that further detailed research would appear momentous. The present review incorporated a detailed account of the plant, stressing its therapeutic uses, pharmacology, mechanism of action based on preclinical and clinical studies, safety issues along with the current research potential of the herbs.

Description of Plants

Physalis are herbaceous plants growing to 0.4 to 3 m tall, similar to the common tomato, a plant of the same family, but usually with a stiffer, more upright stem. They can be either annual or perennial. Most require full sun and fairly warm to hot temperatures. Some species are sensitive to frost, but others, such as the Chinese lantern, *P. alkekengi*, tolerate severe cold when dormant in winter. These plants grow in most soil types and do very well in poor soils and in pots. They require moisture until fruiting. Plants are susceptible to many of the common tomato diseases and pests, and other pests such as aphids, whiteflies, spider mites, and the false potato beetle (*Leptinotarsa juncta*) also attack them. Propagation is by seed. Some species are self-incompatible and require pollen from other plants to bear fruit.[9, 10, 11] Not all *Physalis* species bear edible fruit. Select species are cultivated for their edible fruit, however; the typical *Physalis* fruit is similar to a firm tomato in texture, and like strawberries or pineapple in flavor, with a mild acidity. Some species, such as the Cape gooseberry and tomatillo have been bred into many cultivars with varying flavors, from tart to sweet to savory. *Physalis* fruit are rich in cryptoxanthin.[12] The fruit can be used like the tomato. Once extracted from its husk, it can be eaten raw and used in salads. Some varieties are added to desserts, used as flavouring, made into fruit preserves, or dried and used like raisins. They contain pectin and can be used in pie filling.

A **B** **C** **D**

E

Fig I – A- *Physalis acutifolia,* B - *Physalis peruviana,* C - *Physalis alkekengi,* D –*Physalis angulata,* E- *Physalis minima.*

Active Constituents

Physalis contains biologically active components e.g. physalins, withanolides, phytosterolsand polyunsaturated fatty acids e.g. linoleic acid and oleic acid. Among its major components are high amounts of vitamins A, B and C as well as the presence of essential minerals, magnesium, calcium, potassium, sodium and phosphorus which are classified as macronutrients, while the Iron and Zinc are considered as micronutrients. The fatty acids composition and high amounts of polyunsaturated fatty acids found in oils extracted from physalis species plants. The bioactive phytosterols would give them properties such as antioxidant and hypocholesterolemic effects. Furthermore, the antioxidant activity is due to the high levels of polyphenols and high levels of vitamins A and C. Finally, the presence of exclusive Physalis-gender Physalins and withanolides are steroidal lactones specific from the Solanaceae family have the anti-inflammatory, antimicrobial and anticancer, hepatoprotective or inmunomodulatory and antiparasitic activity. Physalins A, B, D, F and glycosides, which show anticancer activity. Physalins are immunosuppressive substances which are widely used to inhibit unwanted immune responses in autoimmune diseases, allergies and organ

transplants.[2] The fruit of physalis species are highly nutritious, having high levels of vitamins A, B and C.The main active components of vitamin A in fruits are α-carotene, β-carotene and β cryptoxanthin.The Phytosterols are of great interest because of its antioxidant capacity and impact on both total cholesterol and LDL cholesterol.

Mechanisms of Actions Based on Preclinical Studies

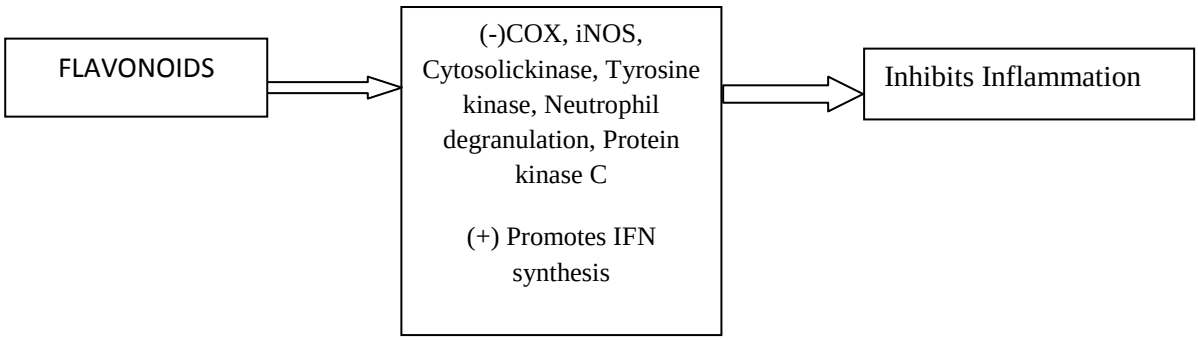
Nephrotoxicity

Physalis extracts have been used traditionally for nephrotoxity and research has been increasingly supportive for these claims. A preclinical study reported that there are various chemicals (xenobiotics) and drugs which cause damage to renal tissues by reactive oxygen species (ROS) production. CCl_4 is known to induce ROS, deplete antioxidant defenses; enzymatic and non-enzymatic substrates; to cause oxidative stress in renal tissues. It was reported that CCl4 metabolized by cytochrome p- 450 generates a highly reactive free radical, and initiates lipid peroxidation of the cell membrane of the endoplasmic reticulum and causes a chain reaction. These reactive oxygen species can cause oxidative damage in DNA, proteins and lipids (Melin *et al.*, 2000). Various studies have demonstrated that CCl4 causes free radical generation in many tissues including kidney. Olagunjua *et al.* (2009) suggested a role for reactive oxygen metabolites as one of the postulated mechanisms in the pathogenesis of CCl_4 nephrotoxicity. It has been hypothesized that physalis extract affords protection by impairing CCl_4 mediated lipid peroxidation, through decreased production of free radical derivatives. The antioxidant effect of Flavonoids that was found in Physalis enhanced the process of regeneration. This might be due to destruction of free radicals, supplying a competitive substrate for unsaturated lipids in the membrane and/or accelerating the repair mechanism of damaged cell membrane. *Physalis peruviana* extract alleviates the nephrotoxicity induced by CCl_4 in albino rats. The protective effects of *Physalis peruviana* are performed through multiple ways. *Physalis peruviana* scavenges free radicals that are produced by CCl_4, increases the activity of antioxidant-defense system and a greater susceptibility of the kidney to oxidant stress might be anticipated. Therefore, Physalis extract may be used as a potential dietary antioxidant to retard aging and preventing diseases caused by ROS or ameliorating oxidative damage in tissues.

Antinociceptive and anti inflammatory properties

The effects of Physalis upon pain and inflammation in rodent models were reported aqueous extract of *Physalis angulata* (10–30 mg/kg) given by i.p. or p.o. route, 0.5 and 1 h prior,

produced significant inhibition of abdominal constrictions caused by acetic acid, with ID50 values of 18.5 (17.4–19.8) and 21.5 (18.9–24.4) mg/kg and inhibitions of 83±8 and 66±5%, respectively. The aqueous extract (10–60 mg/kg, i.p.) also caused significant inhibition of the late-phase of formalin induced pain, with an ID50 value of 20.8 (18.4–23.4) mg/kg and inhibition of 100%. Treatment of mice with (60 mg/kg, i.p.) or with morphine (10 mg/kg, i.p.) produced a significant increase of the reaction time in the hot-plate test. These results demonstrate, for the first time, that the aqueous extract of *Physalis angulata* produce marked antinociception against the acetic acid-induced visceral pain and inflammatory pain responses induced by formalin in mice. The mechanism by which the aqueous extract produces antinociception still remains unclear. However, pharmacological and chemical studies are continuing in order to characterize the mechanism(s) responsible for the antinociceptive action and also to identify the active principles present in *Physalis angulata*. The anti-inflammatory activities of *Physalis angulata* (flower) were determined by carrageenan-induced paw edema, arachidonic acid-induced ear edema and formaldehyde-induced arthritis in mice. The anti-allergic and analgesic activities of these plants were also studied by using 2,4-dinitrofluorobenzene (DNFB)-induced contact hypersensitivity reaction (type IV) and hot plate test in mice, respectively. These plant extracts clearly exhibited inhibitory effects against acute and sub acute inflammation by oral administration (200 mg/kg). Also, administration (200 mg/kg, p.o.) of plant extracts for 1 week significantly inhibited type IV allergic reaction in mice ($P < 0.05$). *Physalis angulata* showed an analgesic effect against hot plate-induced thermal stimulation at a dose of 200 mg/kg. These results provide support for the use of *in* relieving inflammatory pain, and insight into the development of new agents for treating inflammatory diseases.

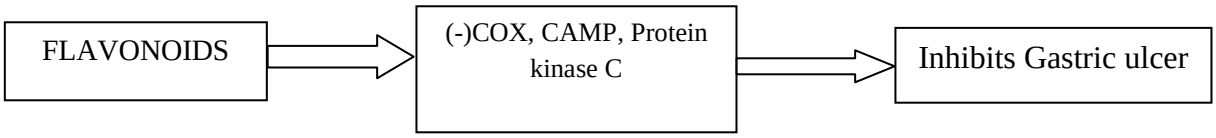


Effect of Flavonoids on Inflammation

Gastric Ulcer

A laboratory study was reported in which methanolic extract of *Physalis minima* leaves was investigated on ethanol induced ulcer models and pylorus ligation in wistar rats[4]. In both

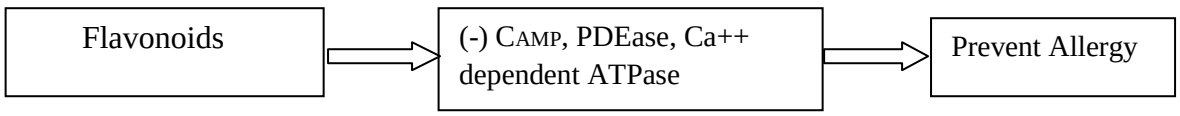
models the common parameter determined was ulcer-index. Methanolic extract of dosage 100, 200mg/kg,p.o produced significant inhibition of gastric lesions induced by pylorus ligation and ethanol induced ulcers. The extract 100mg/kg and 200mg/kg showed significant ($p<0.01$) reduction in gastric volume, free acidity and ulcer index as compared to control. The present study indicates that *Physalis minima* leaves extract have potential anti ulcer activity in both models. This results may further suggests that methanolic extract was found to posses anti-ulcerogenic as well as ulcer healing property, which might be anti secretory activity.



Effect of Flavonoids on Gastric ulcer

Anti asthma

Anti-asthmatic activity of the alcoholic extract of *Physalis angulata* roots in ovalbumin induced experimental mice model. The roots were extracted with ethanol and the anti-asthmatic activity of the extract in ovalbumin-induced asthma in albino mice was evaluated. The parameters assessed were assessment of lung inflammation, OVA-specific immunoglobulin E titre by ELISA and histopathology of lung.[5] The extract (100 and 200 mg/kg I.p) inhibited ovalbumin induced asthma by decreasing releasing of inflammatory mediators. *Physalis angulata* roots extract has potent anti-asthmatic activity. Its anti-asthmatic property probably acts via a reduction in inflammatory mediator's release. Thus the *Physalis angulata* has significant anti-asthmatic property.



Effect of Flavonoids on Asthma

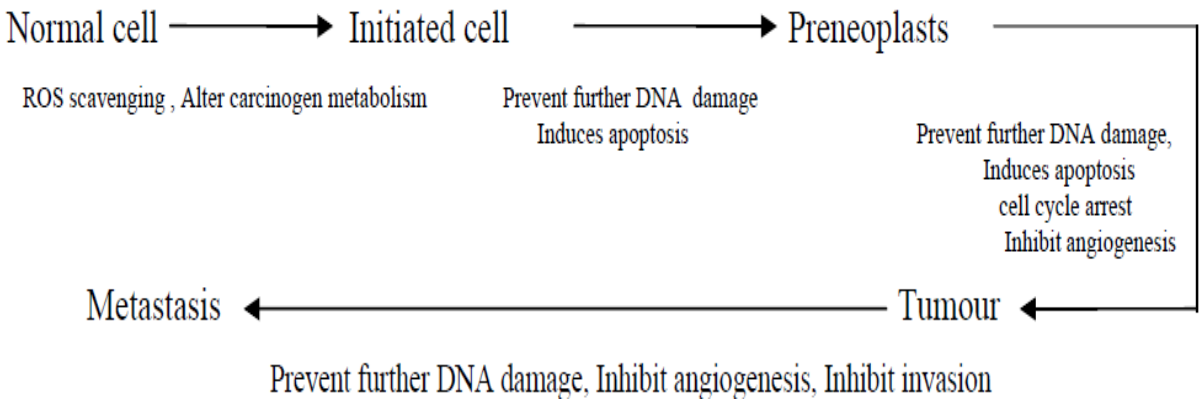
Diuretic effect

Physalis was described to possess Diuretic effect petroleum ether extract of the Physalis minima in albino rats. MEPM (Methanolic Extract of *Physalis minima*) were administered at the doses of 100 and 200 mg/kg, p.o. Furosemide (500 mg/kg, p.o) was used as positive control in study[3]. The diuretic effect of the extract was evaluated by measuring urine volume, sodium and potassium content. Urine volume is significantly increased at two doses of MEPM 100 and 200 mg/kg body wt in treated rats. The excretion of sodium, Potassium

levels was also increased by the MEPM. The diuretic effect of the extract was similar to furosemide. The MEPM had the additional advantage of chloride conserving effect. This study concludes that MEPM produced notable diuretic effect which appeared to be comparable to that produced by the standard diuretic furosemide. It provides a quantitative basis for investigating the use of *Physalis minima* as a diuretic agent.

Anti Cancer effect

Previous studies have suggested that Physalis could be useful in preventing cancer the ethanol extract of Physalis peruviana (EEPP) inhibits growth and induces apoptotic death of human Hep G2 cells in culture, whereas proliferation of the mouse BALB/C normal liver cells was not affected[7]. In this study, we performed detailed studies to define the molecular mechanism of EEPP-induced apoptosis in Hep G2 cells. The results further confirmed that EEPP inhibited cell proliferation in a dose- and time-dependent manner. At 50 mg/ml, EEPP significantly increased the accumulation of the sub-G1 peak (hypoploid) and the portion of apoptotic annexin V positive cells. EEPP was found to trigger apoptosis through the release of cytochrome c, Smac/DIABLO and Omi/HtrA2 from mitochondria to cytosol and consequently resulted in caspase-3 activation. Pre-treatment with a general caspase inhibitor (z-VAD-fmk) prevented cytochrome c release. After 48 h of EEPP treatment, the apoptosis of Hep G2 cells was found to associate with an elevated p53, and CD95 and CD95L proteins expression.[8] Furthermore, a marked down-regulation of the expression of the Bcl-2, Bcl-XL and XIAP, and up - regulation of the Bax and Bad proteins were noted. The results suggest that EEPP-induced Hep G2 cell apoptosis was possibly mediated through the CD95/CD95L system and the mitochondrial signaling transduction pathway.



Effect of Flavonoids on cancer cells

Anti Microbial effect

Physalis is having anti microbial properties the minimum inhibitory concentration of the methanolic extract of *Physalis minima* Methicillin sensitive *Staphylococcus aureus* 0.125 µg/ml, Methicillin resistant *S. aureus* 0.25 µg/ml, Coagulase negative *S. aureus* 0.25-0.5 µg/ml, Vancomycin sensitive *Enterococcus faecalis* 0.5 µg/ml, Vancomycin resistant *Enterococcus Species* 0.125- 0.5 µg/ml, *Moraxella* 2 µg/ml, *Streptococcus Species* 0.125 – 0.25 µg/ml, *H. ınfluenzae* 2-4 µg/ml and against anaerobes is 1-2 µg/ml. Time kill assay were analyzed for methanol extract of *Physalis minima* and it showed bacteriostatic and nonmutagenic activity up to 5 mg per plate in AMES test both in the presence and absence of S9 fraction. Thus, methanol extract of *Physalis minima* exhibited Anti-Microbial activity, which was more active than that of standard linezolid, against a variety of clinically important microorganisms isolated from nearby hospitals in India and nonmutagenic up to 5 mg/plate in AMES test.

Hepatoprotective effect

As Physalis in rich in Flavonoids it is having hepatoprotective effect studies suggest that the aqueous and ethanol extracts prepared from the whole plant of these species were evaluated for their antihepatoma activity.[6] Using XTT assay, three human hepatoma cells, namely Hep G2, Hep 3B and PLC/PRF/5 were tested. The results showed that ethanol extract of P. peruviana (EEPP) possessed the lowest IC50 value against the Hep G2 cells. Interestingly, all extracts showed no cytotoxic effect on normal mouse liver cells.[13, 14] Treatment with carbonyl cyanide m-chlorophenyl hydrazone, a protonophore, caused a reduction of membrane potential (Dcm) by mitochondrial membrane depolarization.[15] At high concentrations, EEPP was shown to induce cell cycle arrest and apoptosis through mitochondrial dysfunction as demonstrated by the following observations: (i) EEPP induced the collapse of Dcm and the depletion of glutathione content in a dose dependent manner; (ii) pretreatment with the antioxidant (1.0 Ag/ml vitamin E) protected cells from EEPP-induced release of ROS; and (iii) at concentrations 10 to 50 Ag/ ml, EEPP displayed a dose-dependent accumulation of the Sub-G1 peak (hypoploid) and caused G0/G1-phase arrest. Apoptosis was elicited when the cells were treated with 50 Ag/ml EEPP as characterized by the appearance of phosphatidylserine on the outer surface of the plasma membrane. The results conclude that EEPP possesses potent antihepatoma activity and its effect on apoptosis is associated with mitochondrial dysfunction.

CONCLUSIONS

The therapeutic potential of this species plants in terms of their efficacy and versatility is such that further detailed research appears crucial. Due to presence of Flavonoids a wide array of biological active compounds that are found abundantly in plant kingdom and dietary intake. They are gaining interest due to their wide variants and number of members.

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