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## **Clinically Tested Medicinal Plant: A Review (Part 1)**

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### **Abstract**

The recent reviews showed that the medicinal plants possessed a wide range of pharmacological activities, but there are few plants which pass the experimental stage to clinical trial. This review was designed to highlight the pharmacological effects of the medicinal plants proved by clinical trials.

*Keywords:* Medicinal plants, Clinical, Trial, therapeutic, effectiveness

### **Introduction**

The standard method which used to prove the efficacy and safety of a treatment is the randomized controlled trial (RCT). The gold standard is considered to be the randomized, double-blind placebo controlled trial (RDPCT). These types of trials are currently used to produce an evidence base for the use of modern drugs. However, recent research model usually concentrated on the testing of single

chemicals, whereas herbs contain many chemicals themselves, and are usually used as part of a mixture of herbs. Many herbs have been trialed as a mixture in this way. However, other studies depend on extraction of a herbal constituent to be used in the clinical trial and many herbal preparations used in such trials are often standardized to contain one constituent of one part of the plant. The recent reviews showed that the medicinal plants possessed a wide range of pharmacological activities[1-76], but there are few plants which pass the experimental stage to clinical trial. This review was designed to highlight the pharmacological effects of the medicinal plants proved by clinical trials.

### ***Agrimonia eupatoria***

A compound herb preparation containing agrimony has been used to treat 35 patients suffering from chronic gastroduodenitis. After 25 days of therapy, 75% of patients claimed to be free from pain, 95% from dyspeptic symptoms and 76% from palpitation pains. Gastroscopy indicated that previous erosion and haemorrhagic mucous changes had healed[77].

The successful treatment of cutaneous porphyria in a group of 20 patients receiving agrimony infusions has been described. An improvement in skin eruptions together with a decrease in serum iron concentrations in urinary porphyrins was noted[78].

### ***Agropyron repens [Elymus repens]***

A post-marketing surveillance was designed to investigate the efficacy and tolerability of a fluid extract of *Agropyron repens [Elymus repens]* (Acorus drops) in patients with urinary tract infections or irritable bladder. Data for 313 patients with urinary tract infections or irritable bladder were analysed. The patients were treated on average for twelve days with 50-60 drops 3 times a day. The primary efficacy criterion was the change of urological symptoms during the course of therapy. Between 69% and 91% of the urological symptoms initially documented were relieved in the course of therapy. Depending on the underlying urological diagnosis, between 32% and 53% of the patients were completely free of symptoms following treatment. Acorus drops were tolerated very well. No adverse drug reactions occurred[79].

In an open clinical trial in 99 patients with micturition disorders (12 female and 87 male), a 20% ethanol fluid extract of *Agropyron repens* was administered for 28-31 days (60 drops 3 times daily). The complaints of urge incontinence, dysuria, nycturia and tenesmus due to adenoma of prostate, prostatitis and cystitis were significantly

reduced in 44.4-100% of patients. Laboratory markers of inflammation (protein, epithelia, leucocytes and erythrocytes in urine) were also normalized. 96% of patients mentioned that the treatment is good or very good. Adverse effects were not recorded. The effect of single and repeated oral administration of the lyophilized aqueous extract of rhizomes of *Agropyron repens* (20 mg/kg) on lipid metabolism was studied in normal and streptozotocin-induced diabetic rats. In normal rats, the aqueous extract induced a significant decrease in the plasma triglycerides concentrations 4 days and 1 week after repeated oral administration. This reduction was abolished 2 weeks after once daily repeated oral administration. A significant decrease of plasma cholesterol levels was observed only 1 week after repeated oral administration. In diabetic rats, the treatment caused a significant decrease in plasma cholesterol after a single and repeated oral administration. A strong decrease in cholesterol levels was observed 6 hours after a single oral administration of the extract. Four days after the repeated oral administration of the extract, the plasma cholesterol level was significantly decreased and remained still diminished after 2 weeks. Repeated oral administration of the aqueous extract of *Agropyron repens* rhizome caused a significant decrease in body weight 2 weeks after oral treatment. In severely hyperglycaemic rats, *Agropyron repens* extract treatment induced reduction of lipid levels and body weight[80].

### ***Allium cepa***

In assessment of hypoglycemic activity of *Allium cepa* in type 1 and type 2 diabetic patients, ingestion of crude *Allium cepa* (100 g) caused a considerable reduction in fasting blood glucose levels by about 89 mg/dl in relation to insulin (145 mg/dl) in type 1 diabetic patients and it reduced fasting blood glucose levels by 40 mg/dl, compared to glibenclamide (81 mg/dl) in type 2 diabetic patients, 4 hours later. The same dose of crude *Allium cepa* produced a significant reduction in the induced hyperglycemia (GTT) by about 120 mg/dl compared to water (77 mg/dl) and insulin (153 mg/dl) in type 1 diabetic patients and considerably reduced GTT by 159 mg/dl in relation to water (55 mg/dl) and glibenclamide (114 mg/dl) in type 2 diabetic patients, after 4 hours[81].

### ***Allium sativum***

Eating of 10 g fresh garlic per day for 2 months significantly decreases (15%-28.5%) serum cholesterol levels among hypercholesterolemic patients[82]. Garlic oil caused a steady decrease in LDL and VLDL levels with concomitant increase in HDL levels[83-84].

Intake of enteric-coated garlic powder (equal to 400 mg garlic, 1mg allicin)

twice daily in hyperlipidemic patients has significantly reduced total cholesterol, LDL-cholesterol and triglyceride and increased HDL-cholesterol[85].

The level of cholesterol, triglyceride, phospholipids and  $\beta$ - lipoproteins were significantly declined in the individuals consuming 10-50 g of garlic /week. These results indicate that routine consumption of garlic in the diet has a beneficial effect in maintaining the serum lipids at low or normal levels[86]. In a placebo-controlled trial of patients with stage II peripheral arterial occlusive disease, garlic powder supplements, 800 mg daily were associated with a significant increase in walking distance by 46 meters; the improvement started after the fifth week of treatment[87]. Patients treated with 900 mg daily of standardized garlic powder showed 9-18% reduction in plaque volume, a 4% decrease in LDL levels, an 8% increase in HDL concentrations, and a 7% decrease in blood pressure[88].

Clinical studies showed that garlic produced hypotensive effects. Garlic induced significant reduction in systolic and diastolic blood pressure. The authors postulated that the hypotensive action of garlic is due to a direct relaxant effect on smooth muscles[89-96].

On the other hand, oral administration of garlic powder (800mg/day) to 120 patients for 4 weeks in a double-blind, placebo-controlled study decreased the average blood glucose by 11.6 % [97].

The therapeutic efficacy of (garlic 10% in petrolatum) was compared with (sulphur 10% in petrolatum) in 106 patients with scabies in three primary health care centers. It was found that the efficacy of sulphur 10% in petrolatum was (100%), while the efficacy of garlic 10% in petrolatum was (83.33%.) [98].

### ***Aloe vera***

A significantly faster healing time and a higher number of healed lesions than the placebo was recorded in a randomized, controlled double blind clinical trial of 60 men suffering from an initial episode of Herpes simplex infection, treated with an *Aloe vera* extract (0.5%) in a hydrophilic cream [99].

A clinical study showed that *Aloe vera* gel might be helpful in treating patients with duodenal ulcers [100-101].

Five thousand patients of atheromatous heart disease, presented as angina

pectoris, were studied over a period of five years. After adding the (Husk of Isabgol) and (*Aloe vera*) (an indigenous plant known as ghee-guar-ka-paththa) to the diet, a marked reduction in total serum cholesterol, serum triglycerides, fasting and postprandial blood sugar level in diabetic patients, reduction of total lipids and an increase in HDL were noted. Simultaneously the clinical profile of these patients showed reduction in the frequency of anginal attacks[102].

Orally administered *Aloe gel* (1-2 tablespoons twice daily) enhanced the hypoglycemic effect of glibenclamide[103-104].

### ***Alpinia galanga***

In a randomized double-blind placebo controlled study, patients with osteoarthritis of the knee and moderate-to severe pain, the concentrated extract has been found significantly reduce symptoms of osteoarthritis [105].

### ***Althaea officinalis***

In a double blind clinical study, Rouhi and Ganji used *Althaea officinalis* in patients with hypertension who had been developed cough during taking of angiotensin converting enzyme inhibitors. The patients received 40mg of *Althaea officinalis* three times daily as 20 drops for four weeks. The Mean scores of the severity of the cough in the group which have been treated by *Althaea officinalis* had a significant change from the score of 2/66+0.958 (to) 1/23+1.006. Eight patient in the *Althaea officinalis* group showed almost complete cough abolition[106].

### ***Ammi majus***

Numerous studies have assessed the efficacy of Fructus *Ammi majus* and xanthotoxin for the treatment of vitiligo, psoriasis, and hypopigmentation tinea versicolor [107-116].

Experimentation with *Ammi majus* extracts was started in Egypt by El Mofti<sup>109,116</sup>. This followed by the work of Sidi and Bourgeois who used *Ammi majus* Linn, in six patients with vitiligo, five men and one woman. Their ages were from 30 to 50 years. *Ammi majus* Linn was used (a) by oral administration, (b) by local topical application at the affected sites followed by sun or ultraviolet lamp exposure, or, (c) by a combination of (a) and (b). Three of patients were subjected to the combined treatment, two only to topical treatment and one to treatment by mouth for 5 months, and then to the combined treatment. The repigmentation appeared in all

patients as pigmented minute macules with hair follicles in their center. These macules were distributed over the leukodermic plaques and increased progressively in size until they joined, forming larger islands. This was particularly distinct in the lesions on the trunk and on the extremities. On the face the repigmentation developed more rapidly and appeared to be progressing more from the periphery towards the center[117].

Many clinical trials were carried out to investigate the efficacy of *Ammi majus* in vitiligo. Patient with leukodermis took oral *Ammi majus* powdered fruits with exposing the affected patches to direct sunlight for 1 hour developed symptoms of itching, redness, oedema, vesiculation and oozing in the leukodermic patches. Within few days, the affected skin gradually started to display deep brown pigmentation[118].

In two small group of patients (eight patients each) with leukoderma treated with oral(0.05 g of *Ammi majus* three time daily) or liniment 1 g/100 ml, applied to the skin, with daily exposure of leukodermic areas to the sun for 0.5 hour or to UV light for 2 minutes, gradually increasing to 10 minutes, the leukodermic skin areas were inflamed and vesiculated, and the leukodermic areas began to show normal pigmentation[108].

However *Ammi majus* and its furanocoumarins constituents showed good results in many other clinical studies, 70% of the patients treated with an oral dose of 0.6 mg/kg bw of xanthotoxin 2 hours before exposure to sunlight three times per week with calcipotriol ointment in a randomized double-blind study, showed significant improvement[119].

Xanthotoxin with exposure to either UV-A or UV-B radiation for the treatment of plaque psoriasis in 100 patients appeared effective in reducing the number of plaques[120]. Oral administration of 0.6 mg/kg bw of xanthotoxin with two UV-A radiation dosage regimens was used for treatment of patients with moderate–severe chronic plaque psoriasis. 42% of patients were clear 1 year after treatment and the treatment regimens were well tolerated[121].

Many other similar results were obtained in assessment of *Ammi majus* and its furanocoumarins in the treatment of psoriasis, vitiligo and tinea versicolor by many authors[108,115,122-123].

### ***Ammi visnaga***

A clinical trial of khellin in 38 cases of angina pectoris and in 8 cases of

coronary thrombosis was performed . Continuous treatment, by the oral or intramuscular routes or by both, gave favourable results in 35 out of 38 cases of angina pectoris. Continuously administration of khellin for several weeks to eight patients after coronary thrombosis appeared favourable[124].

A clinical study was carried out on 20 non-obese, normolipaemic male subjects to determine the effects of orally administered 50 mg khellin four times daily for 4 weeks on the plasma lipids. Plasma total cholesterol and triglyceride remained unchanged, but high-density-lipoprotein cholesterol concentration was significantly elevated during the treatment and till one week after cessation of treatment[125]. In a comparison with glyceryl trinitrate, khellin (3 ml. containing 150 mg. of khellin, alcoholic extract standardized to contain 50 mg/ml) was used in twelve patients for prevention of angina of effort and the electrocardiographic changes that may accompany it. Khellin was less potent but longer acting than glyceryl trinitrate, and it did not cause any unpleasant side effects[126].

A double-blind, placebo-controlled study of 60 people indicated that the combination of oral khellin (which is the main constituent of *Ammi visnaga*) and natural sun exposure caused repigmentation in 76.6% of the treatment group, in comparison, no improvement was seen in the control group receiving sunlight plus placebo[127].

A subsequent placebo-controlled study of 36 patients of vitiligo , showed that a topical khellin gel plus UVA caused repigmentation in 86.1% of the treated cases, as opposed to 66.6% in the placebo group[128].

### ***Anthemis nobilis***

In an open clinical study carried out on 54 patients with chronic bronchial asthma, *A. nobilis* showed antiasthmatic effects, it caused significant elevation in the values of forced expiratory volume in first second (FEV<sub>1</sub>) and forced volume capacity (FVC) with marked reduction in asthmatic attacks[129].

### ***Arctium lappa***

Silver *et al* investigated the effect of burdock powder on normal and diabetic patients, and found out that burdock root possess hypoglycemic effects. The antidiabetic effects of burdock root was related to polysaccharides, the main component of the root . Root extract maintained the blood glucose level constant, therefore improving the tolerance to high glucose level[130].

***Aristolochia maurorum***

Aristolochic acid is toxic in human, it caused rapidly progressive interstitial nephritis leading to end-stage renal disease and urothelial malignancy, it was originally reported in Belgium in patients ingested slimming pills containing powdered root extracts of *Aristolochia* Spp[131-134]. The initial presentation of Aristolochic acid nephropathy was usually silent and the renal failure was discovered by routine blood testing. However, few cases presenting with an acute renal failure due to tubular necrosis[135-139].

***Astragalus tribuloides***

Astragalus injection was effective in lowering  $\beta(2)$ -microglobulin, microalbuminuria compared with placebo, and it was also superior to prostaglandin in lowering blood urea nitrogen, creatinine clearance rate. There were no adverse effects reported in the trials from astragalus injection[140].

***Avena sativa***

In overweight patients, beta glucan from oats has been shown to decrease hypertension. Avenanthramide is an oat polyphenol that has been shown to enhance production of nitric oxide, a potent vasodilator, and to inhibit thickening of vascular smooth muscle. Both actions are preventative to developing atherosclerosis[141-142].

A clinical trial was carried out to confirm the anti-obesity effect of oat. Subjects with BMI  $\geq 27$  and aged 18-65, were randomly divided into a control (n=18) and an oat-treated (n=16) group, taking a placebo or beta glucan-containing oat cereal, respectively, for 12 weeks. The result showed that consumption of oat reduced body weight, BMI, body fat and the waist-to-hip ratio. Profiles of hepatic function, including AST and ALT showed decrements in patients with oat consumption. Nevertheless, anatomic changes were not observed by ultrasonic image analysis. Ingestion of oat was well tolerated and there was no adverse effect during the trial[143].

***Bacopa monnieri***

A clinical trial was carried out to assess the effects of 12-weeks administration of *Bacopa monnieri* (300mg/day) on memory performance in people over the age of 55-years. Bacopa significantly improved memory acquisition and retention in older



persons[144]. Significant cognitive enhancing benefits have been demonstrated with chronic administration of Bacopa extracts. A double-blind, placebo-controlled, 12-week trial utilizing the same patient selection criteria and the same dose of Bacopa extract (300 mg daily) containing 55% combined bacosides, was carried out. Forty-six healthy volunteers (ages 18-60) were randomly and evenly divided into treatment and placebo groups. The same series of tests administered in the acute dosage trial were administered at baseline, five, and 12 weeks after treatment began. At the end of the 12-week study, results indicated a significant improvement in verbal learning, memory consolidation, and speed of early information processing in the treatment group compared to placebo. These effects were not observed at baseline or at five weeks[145].

The Bacopa supplement was commercially available as KeenMind™ (Flordis). This product is manufactured from the stems, leaves and roots of Bacopa and is extracted with 50% ethanol. It is standardized to contain active bacosides at levels of 55% ± 5%. KeenMind™ help develop novel preventative health practices and nutritional/ pharmacological targets in the elderly for cognitive and brain health. Bacopa appeared to have multiple modes of action in the brain, all of which may be useful in ameliorating cognitive decline in the elderly. These include: (i) direct cholinergic action; (ii) anti-oxidant (flavonoid) activity; (iii) metal chelation; (iv) anti-inflammatory effects; (v) improved blood circulation; (vi) adaptogenic activity; and (vii) removal of b-amyloid deposits[146]. However, in a double-blind randomized, placebo control study performed on 76 adults aged between 40 and 65 years, in which various memory functions were tested and levels of anxiety was measured, the rate of learning was unaffected by *Bacopa monnieri* suggesting that *Bacopa monnieri* decreases the rate of forgetting of newly acquired information. Tasks assessing attention, verbal and visual short-term memory and the retrieval of pre-experimental knowledge were unaffected. Questionnaire measures of everyday memory function and anxiety levels were also unaffected[147].

A double-blind, randomized, placebo controlled trial of 169 patients with irritable bowel syndrome, effects of an Ayurvedic preparation containing *Bacopa monniera* and *Aegle marmelos* was compared with standard therapy (clidinium bromide, chlordiazepoxide, and psyllium). Subjects were randomly assigned to standard drug treatment, botanical treatment, or placebo for six weeks. Treatment was administered orally as drug, botanical, or placebo three times daily. Ayurvedic therapy was superior to placebo, however, the two botanicals were not given separately, and the benefit could not link specifically to the Bacopa portion of the Ayurvedic preparation[148].

### ***Bellis perennis***

The effect of *Bellis perennis* on postpartum blood loss was studied by double blind, placebo-controlled, randomized, clinical trial. At 72 h postpartum, mean Hb levels remained similar after treatment with homeopathic remedies (12.7 versus 12.4) as compared to a significant decrease in Hb levels in the placebo group (12.7 versus 11.6;  $p < 0.05$ ), in spite of less favorable initial characteristics of the treatment group. The mean difference in Hb levels at 72 h postpartum was -0.29 (95% CI -1.09; 0.52) in the treatment group and -1.18 (95% CI -1.82; -0.54) in the placebo group ( $p < 0.05$ ) [50]. *Bellis perennis* showed haemolytic activity. It has been found that the haemolytic activity of the drug changes in dependence on the time of collection of capitula during the year; it is lowest in March, then it increases, reaching the maximum in summer months (June, July, August), and then it decreases again [149]. In two placebo-controlled studies, Traumeel injections, (which contains *Bellis perennis*) was used in patients with hemarthrosis. It showed that Traumeel injections improved joint and mobility, and decreased intensity of pain and effusion [150-151].

### ***Benincasa hispida***

Salad was prepared by using 100gm of ash gourd (*Benincasa hispida*) and one gram of curry leaves (10 curry leaves) and five grams of skimmed milk powder (made into curd) and pepper and salt are added for taste. This salad was freshly prepared every day and given to hyperlipidemic diabetic patients in mid morning for a period of three months to find out the therapeutic effect of supplementation of ash gourd and curry leaves. Supplementation of ash gourd and curry leaves had significant hypoglycemic and hypolipidemic effect and it reduced the blood glucose level (both fasting and post prandial), within the period of three months [152].

### ***Bidens tripartite***

500 patients with dysentery, 65 with acute enteritis and 248 with chronic enteritis were used the aerial parts of the plant. Several different dosage forms of the herb were used: 200 g of fresh whole herb and 100 g of dried herb in decoctions (in three divided doses per day); granules containing 5 g of dried aqueous extract, three times daily; 0.5 g tablets of dried aqueous extract, 10 tablets each time three times daily; and injection, 2 ml per injection (dose not stated), 2–3 times daily. The herbal preparations were administered for 3–10 days to patients who already had diarrhoea. 387 of the 500 patients with chronic dysentery were reported to have been cured, 13 had not responded within 3 days. All 313 patients with enteritis were reported to have been cured [153].

Clinically, 70% ethanol extract of the aerial parts of the plant and an ointment containing 2.5% of the extract were used by 53 patients with psoriasis. After one week of oral administration of the extract (20 drops three times daily) with application of the ointment to the affected areas of the skin once a day, desquamation of the skin was decreased, and a decoloration of the psoriatic plaques was observed. 29 of the patients were clinically recovered, 22 patients were clinically improved and failure of the therapy was recorded in 2 patients[154].

### ***Bryophyllum calycinum***

A prospective double-blind trial with orally applied Bryophyllum versus placebo was carried out. Thirty-two patients divided into two groups, 15 patients received Bryophyllum and 17 received the placebo. The time of delivery did not differ between the groups. In both groups the mean time of birth was in the 35 week of gestation. The mean birth weight was slightly higher in the placebo group (2192 g) compared to the Bryophyllum group (1948 g). A transition to the intensive care unit was slightly higher in the placebo group (13) compared to the Bryophyllum group(11)[155].

### ***Calendula officinalis***

The therapeutic efficacy of marigold (*Calendula officinalis*) extract was investigated in the epithelialization of lower leg venous ulcers. Twenty-one patients with 33 venous ulcers out of 34 patients were treated with (*Calendula officinalis* ointment) which applied twice a day for 3 weeks. The second group was a control group that consisted of 13 patients with 22 venous ulcers. In the control group, saline solution dressings were applied to ulcers for the same period. In the experimental group the total surface of all the ulcers at the beginning of the therapy was 67,544 mm<sup>2</sup>. After the third week the total surface of all the ulcers was 39,373 mm<sup>2</sup> (a decrease of 41.71%). In seven patients, complete epithelialization was achieved. In the control group the total surface of all the ulcers at the beginning of the therapy was 69,722 mm<sup>2</sup>. After the third week the total surface of all the ulcers was 58,743 mm<sup>2</sup> (a decrease of 14.52%). In four patients, complete epithelialization was achieved. There was a statistically significant acceleration of wound healing in the experimental group ( $p < 0.05$ )[156].

The effect of *Calendula officinalis* flowers extract mouthwash as oral gel (by maceration in ethanol 70% for a 72 hour period) was evaluated in radiation-induced oropharyngeal mucositis (OM) in patients with head-and-neck cancer. Forty patients

with neck and head cancers under radiotherapy or concurrent chemoradiotherapy protocols were receive either 2% calendula extract mouthwash or placebo. Patients were treated with telecobalt radiotherapy at conventional fractionation (200 cGy/fraction, five fractions weekly, 30–35 fractions within 4–7 weeks). The oropharyngeal mucositis was evaluated by the oral mucositis assessment scale (OMAS). Calendula mouthwash significantly decreased the intensity of OM compared to placebo at week 2 (score: 5.5 vs. 6.8,  $p = 0.019$ ), week 3 (score: 8.25 vs. 10.95,  $p < 0.0001$ ) and week 6 (score: 11.4 vs. 13.35,  $p = 0.031$ )[157].

170 patients with duodenal ulcers and/or gastroduodenitis, treated with a herbal combination containing calendula showed improvement of symptoms in 90%. 24 adults with non-specific colitis treated with herbal tea included calendula, showed improved symptoms in 96% of the patients within two weeks[158].

### ***Calotropis procera***

Topical preparation of *C. procera* was used for the treatment of eczema in 94 patients. The trials were conducted for nine months. The result was found encouraging, complete cure of all the signs and symptoms have been noted in 14 (14.89%) patients, excellent response was noted in 24 (25.53%) patients, good response in 33 (35.10%) patients, fair response in 10 (10.63%) patients. Two (2.12%) patients showed poor response to the treatment and 2 (2.12%) patients exhibited worsened condition[159].

### ***Carthamus tinctorius***

The therapeutic and preventive effects of Safflower Injection (AI) in vascular crisis after free flap transplantation was studied clinically. Sixty patients undergoing free flap transplantation were randomly assigned to the treatment group and control group, thirty in each. Free flap transplantation was performed on all patients, and medication was given 0.5h before flap vascular anastomosis, 1-7 days after surgery. Twenty ml AI was intravenously dripped to patients in the treatment group after adding in 250 ml 5% glucose injection, while Dextran-40 was intravenously dripped to patients in the control group. The medication was conducted once per day. The hemorheology and four indices of blood coagulation [prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen] were compared between the two groups before operation (T0), during operation (T1), 24 h after operation (T2), three days after operation (T3), and seven days after operation (T4). Meanwhile, flaps were observed and adverse reaction recorded. The clinical efficacy and safety were compared. Better result was obtained in the treatment group when

compared their clinical efficacy (86.67% vs 60.00%,  $P < 0.05$ ). The whole blood high and low viscosity, plasma viscosity, red blood cell volume, RBC aggregation index all decreased, and RBC deformed index increased in the two groups at T4, showing statistical difference when compared with those at T3 ( $P < 0.05$ ,  $P < 0.01$ ). There was no statistical significance in the four indices of blood coagulation when compared with any time point in the same group ( $P > 0.05$ ). There was no statistical significance in hemorheology and the four indices of blood coagulation between the two groups at the same time point ( $P > 0.05$ ). The adverse reaction rate in the treatment group was lower than that in the control group, showing statistical difference (13.33% vs 30.00%,  $P < 0.05$ )[160].

The effects of long-term supplementation with Safflower seed extract (SSE) on arterial stiffness in human subjects were evaluated in a double blind clinical trial. 77 males (35-65 years) and 15 postmenopausal females (55-65 years) with high-normal blood pressure or mild hypertension who were not undergoing treatment received SSE (70 mg/day as serotonin derivatives) or placebo for 12 weeks, and pulse wave measurements, ie, second derivative of photoplethysmogram (SDPTG), augmentation index, and brachial-ankle pulse wave velocity (baPWV) were conducted at baseline, and at weeks 4, 8, and 12. Vascular age estimated by SDPTG aging index, improved in the SSE-supplemented group when compared with the placebo group at four ( $P = 0.0368$ ) and 12 weeks ( $P = 0.0927$ ). The trend of augmentation index reduction ( $P = 0.072$  versus baseline) was observed in the SSE-supplemented group, but reduction of baPWV by SSE supplementation was not observed. The SSE-supplemented group also showed a trend towards a lower malondialdehyde-modified-LDL autoantibody titer at 12 weeks from baseline[161].

### ***Carum carvi***

The effect of the *Carum carvi* plant on resumption of bowel motility after Cesarean section was investigated by a randomized controlled pilot study conducted on 20 women undergoing elective Caesarean section under general anesthesia. The patients were randomly divided into two groups. The intervention group drank 10 ml of *Carum carvi* syrup containing 2 g of *Carum carvi* in 20 ml of syrup at 8 to 8 $\frac{1}{2}$  hours after surgery. The control group was given 10 ml of the placebo syrup at 8 to 8 $\frac{1}{2}$  hours after surgery. Demographic characteristics, time of first peristaltic, first gas passage, first bowel movement, and time until hospital discharge were compared for the two groups. The results showed that compared to the control group, the intervention group had significantly shorter mean interval of the first intestinal sounds

( $10.0 \pm 2.03$  h vs.  $19.28 \pm 3.95$  h); mean time to first passage of flatus ( $15.91 \pm 3.73$  h vs.  $26.82 \pm 5.83$  h), mean time to first bowel movement ( $20.31 \pm 4.63$  h vs.  $31.7 \pm 10.2$  h) and mean length of hospitalization ( $31.71 \pm 7.57$  h vs.  $50.6 \pm 16.49$  h) ( $p < 0.05$ ). There were no serious side effects associated with consumption of the syrup. Accordingly, the use of *Carum carvi* after caesarean section can speed the resumption of post-operative bowel motility[162].

The efficacy and safety of a herbal preparation STW 5-II containing extracts from bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root and lemon balm was investigated in the treatment of 120 patients with functional dyspepsia. During the first 4 weeks, the gastrointestinal symptom score (GIS) was significantly decreased in subjects on active treatment compared to the placebo ( $p < 0.001$ ). During the second 4-week period, symptoms further improved in subjects who continued on active treatment or who switched to the active treatment ( $p < 0.001$ ), while symptoms deteriorated in subjects who switched to placebo. After 8 weeks 43.3% on active treatment and 3.3% on placebo reported complete relief of symptoms. ( $p < 0.001$  vs. placebo)[163].

*Carum carvi* elevated TSH level, high TSH levels was recorded in few patients with thyroid cancer who receiving *Carum carvi* despite being on suppressive dose of levothyroxin. TSH level returned to normal after discontinuation of the *Carum carvi*[164].

#### **Date palm: *Phoenix dactylifera***

Pollen of Date palm (500 mg iq) and a combination of zinc sulphate & pollen of Date palm (500 mg iq) in infertile men significantly increased serum LH, FSH, & testosterone levels. It was also, increased significantly sperm count & motility. Sexual desire was also significantly increased. Wives of treated men got pregnancy during the treatment period[76,165].

#### **Conclusion**

This review discussed the clinically tested medicinal plant to open the door for their clinical uses as a result of effectiveness and safety.

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