Natural Product Radiance, Vol. 7(4), 2008, pp.364-373

Review Paper

Review on nutritional, medicinal and pharmacological properties of Papaya (*Carica papaya* Linn.)

K L Krishna[1]*, M Paridhavi[2] and Jagruti A Patel[3]

[1]JSS College of Pharmacy, SS Nagara, Mysore-570 015, Karnataka, India

[2]Rajiv Gandhi Institute of Pharmacy, Trikarpur-671 310, Kasargod District, Kerala, India

[3]Institute of Pharmacy, Nirma University of Science & Technology, Ahmedabad-382 481, Gujarat, India

*Correspondent author, E-mail: krishpharm@rediffmail.com

Phone: 0821-249 7583, 249 5900; +91-9886610010 (Mob.)

Received 31May 2007; Accepted 7April 2008

Abstract

Papaya (***Carica papaya* Linn.**) is commonly known for its food and nutritional values throughout the world. The medicinal properties of papaya fruit and other parts of the plant are also well known in traditional system of medicine. Since, each part of papaya tree possesses economic value, it is grown on commercial scale. During the last few decades considerable progress has been achieved regarding the biological activity and medicinal application of papaya and now it is considered as valuable nutraceutical fruit plant. It can be chosen as a source of papain for the development of various industrial and pharmaceutical products. In the present review nutritional value of the fruit and medicinal properties of its various parts have been discussed to provide collective information on this multipurpose commercial fruit crop.

Keywords: Papaya, *Carica papaya*, Medicinal plant, Nutraceutical, Fruit, Papain.

IPC code; Int. cl.[8]—A61K 36/00, A23L 1/00

Introduction

The papaya tree belongs to a small family — Caricaceae having four genera in the world. The genus ***Carica* Linn.** is represented by four species in India, of which ***Carica papaya* Linn.** is the most widely cultivated and best-known species. Among the other species, ***C. cauliflora* Jacq.**, ***C. pubescens* Lenne & K. Koch** and ***C. quercifolia* Benth. & Hook.f. ex Hieron.** are possible sources of breeding material for inducing frost and virus resistance in cultivated papaya. The fruits, leaves and latex obtained from papaya plant are used medicinally and for various other purposes. Papain, a major chemical compound extracted from fruit and stem latex is used in brewing and wine making and in the textile and tanning industries[1-3]. Papaya contains broad spectrum of phytochemicals including, polysaccharides, vitamins, minerals, enzymes, proteins, alkaloids, glycosides, fats and oils, lectins, saponins, flavonoids, sterols, etc. (Table 1)[1,3,4].

The present paper deals with origin and distribution, brief morphological characters, nutritional value and results of reported research findings on its medicinal properties.

Origin, Distribution and Morphology

Papaya is probably originated in southern Mexico and Costa Rica, subsequently it was introduced as a plantation crop in Australia, Hawaii, Philippines, Sri Lanka, South Africa, India and in all tropical and subtropical regions. It is grown both commercially and in home gardens. Papaya is a polygamous species and it is difficult to identify a plant whether it is male, female or hermaphrodite. It is a tree reaching 3-10 m in height, with the habit of a palm; the fleshy stem marked by scars where leaves have fallen off, is surmounted by a terminal panache of leaves on long petioles and with 5-7 lobes. Flowers fragrant, trimorphous, usually unisexual-dioecious, male flowers in lax many-flowered, densely pubescent cymes at the tips of the pendulous, fistular rachis; female flowers large, solitary or in few flowered racemes,

Table 1: Chemical composition of various parts of Papaya plant[1, 3, 4]

Part	Constituents
Fruits	Protein, fat, fibre, carbohydrates, minerals: calcium, phosphorous, iron, vitamin C, thiamine, riboflavin, niacin, and carotene, amino acids, citric and malic acids (green fruits), volatile compounds: linalool, benzylisothiocyanate, *cis* and *trans* 2, 6-dimethyl-3,6 epoxy-7 octen-2-ol, Alkaloid, α; carpaine, benzyl-β-D glucoside, 2-phenylethyl -β-D-glucoside, 4-hydroxy-phenyl-2 ethyl-β-D-glucoside and four isomeric malonated benzyl-β-D-glucosides.
Juice	N-butyric, n-hexanoic and n-octanoic acids, lipids; myristic, palmitic, stearic, linoleic, linolenic and *cis*-vaccenic and oleic acids.
Seed	Fatty acids, crude protein, crude fibre, papaya oil, Carpaine, benzylisothiocyanate, benzylglucosinolate, glucotropacolin, benzylthiourea, hentriacontane, β-sitosterol, caricin and an enzyme myrosin.
Root	Carposide and an enzyme myrosin.
Leaves	Alkaloids carpain, pseudocarpain and dehydrocarpaine I and II, choline, carposide, vitamin C and E.
Bark	β-Sitosterol, glucose, fructose, sucrose, galactose and xylitol.
Latex	Proteolytic enzymes, papain and chemopapain, glutamine cyclotransferase, chymopapains A, B and C, peptidase A and B and lysozymes.

with a short thick rachis, fruit a large berry, varying widely in size, elongate to globose with a large central cavity, seeds black, tuberculous and enclosed in a transparent aril. The fruit bearing trees are less than 18 month old. The leaves and unripe fruit contain milky juice in which the protein ferment papain is present[1-3].

Nutritional value

Papaya is a common man's fruit, which is reasonably priced and has a high nutritive value. It is low in calories and rich in natural vitamins and minerals. Papaya places first among the fruits for vitamin C, vitamin A, riboflavin, folate, calcium, thiamine, iron, niacin, potassium and fibre. The comparative low calories content (32 kcal/100g of ripe fruit) makes this a favourite fruit of obese people who are into weight reducing regime. Papaya has more carotene compared to other fruits such as apples, guavas, sitaphal and plantains, which help to prevent damage by free radicals. Unripe green papaya is used as vegetable, it does not contain carotene but all other nutrients are present (Table 2). It is also used in salads, pies, sherbets, juices and confections. Papaya when consumed regularly will ensure a good supply of vitamin A and C, which are essential for good health especially for eyesight and can help to prevent early age blindness in children. The fruit is a rich source for different types of enzymes. Papain, vegetable pepsin present in good amount in unripe fruit is an excellent aid to digestion, which helps to digest the protein in food at acid, alkaline or neutral medium. Thus, it can be prescribed for dyspeptic patients, as papain may help in the digestion of proteins. The celiac disease patients, who cannot digest the wheat protein gliandin, can tolerate it, if it is treated with crude papain. Papaya has the property of tenderizing meat. This knowledge is being put to use by cooking meat with raw papaya to make it tender and digestible[3, 5].

The fermented papaya fruit is a promising nutraceutical as an antioxidant. It improves the antioxidant defence in elderly patients even without any overt antioxidant deficiency state at the dose of 9g/day orally[6, 7]. The papaya lipase, a hydrolase enzyme tightly bonded to the water insoluble fraction of crude papain, is considered as a "naturally immobilized" biocatalyst[8].

The dried fruit skin is a potential source as dietary ingredient for broiler chickens, it gives similar food consumption, food conversion efficiency, survivability and meat yields to a control diet when used up to 120g/kg of diet[9]. Fouzder SK *et al* have reported that, dried papaya skin could safely be used up to

Table 2 : Nutritive value of 100g of Papaya fruit[5]

Constituents	Ripe papaya	Green papaya
Protein	0.6 g	0.7 g
Fat	0.1 g	0.2 g
Minerals	0.5 g	0.5 g
Fibre	0.8 g	0.9 g
Carbohydrates	7.2 g	5.7 g
Energy	32 kcal	27 kcal
Total carotene	2,740µm	0
Beta carotene	888 µm	0

90g/kg in the diet of growing pullets[10]. The papaya seed is also used in the ethnoveterinary practices[11].

Effective antioxidant supplementation Bionormalizer, a natural Japanese health food prepared by the fermentation of papaya, is able to improve the haemorrheology in alcoholics either by directly affecting the ethanol related lipoperoxidation and xanthine oxidase system activation and/or by modifying red blood cell membrane characteristics[12]. It also exhibits therapeutic properties against various pathological disorder including tumours and immunodeficiency. Its protective action is based on the free radical scavenging activity as well as normalization of an organism's superoxide level. It is proposed that, normalization of an organism's superoxide level, which is due to inactivation of the ferrous ions, the catalyst of the superoxide driven Fenton reaction, is one of the molecular mechanism of Bionormalizer activity[13,14]. Papaya markedly increases iron (Fe) absorption from rice meal, which was measured in parous Indian women, using the erythrocyte utilization of radioactive Fe method[15]. The fruit is rich in vitamins, minerals, proteins, polysaccharides, lectins, saponins and flavonoids, and can be used in the prevention of complications of diabetes mellitus[16]. The black seeds are edible and have a sharp, spicy taste. They are sometimes ground up and used as a substitute for black pepper. In some parts of Asia the young leaves of papaya are steamed and eaten like spinach[3-4].

Medicinal and Pharmacological properties

Many biologically active phytochemical(s) have been isolated from papaya and studied for their action, recently an antifungal chitinase has been gene cloned and characterized from papaya fruit. The chitinase is classified as class IV chitinase based on its amino acid sequence homology with other plant chitinases. The recombinant papaya chitinase also has antibacterial activity[17]. The purified chemopapain from commercially available spray dried latex of the fruits has shown immunological properties[18]. The anthelmintic activity of papaya seed has been variously ascribed to carpaine (an alkaloid) and carpasemine (later identified as benzyl thiourea) and benzylisothiocyanate[19], cysteine proteinases from papaya fruit have also been reported[20]. Carpaine, an alkaloid with an intensively bitter taste and a strong depressant action on the heart, has been obtained from the fruit and seed, but especially from the leaves[21].

Various pharmacological action(s) and medicinal uses of different parts of papaya are well reported in the ancient literature[3, 21, 22]. Some of them especially Ayurvedic have been summarized in Table 3. Biological activities of papaya are reported with the crude extracts and different fractions from latex, seed, leaf, root, stem bark and fruit. However, crude extracts of different parts of papaya have been used as traditional medicine for the treatment of various diseases. However, apart from these, there

Table 3 : Some medicinal uses of Papaya plant as mentioned in ancient Ayurvedic literature[3, 21, 22]

Part	Medicinal uses
Latex	Anthelmintic, relieves dyspepsia, cures diarrhoea, pain of burns and topical use, bleeding haemorrhoids, stomachic, whooping cough.
Ripe fruits	Stomachic, digestive, carminative, diuretic, dysentery and chronic diarrhoea, expectorant, sedative and tonic, relieves obesity, bleeding piles, wounds of the urinary tract, ringworm and skin diseases psoriasis.
Unripe fruit	Laxative, diuretic, dried fruit reduces enlarged spleen and liver, used in snakebite to remove poison, abortifacient, anti-implantation activity and antibacterial activity.
Seeds	Carminative, emmenagogue, vermifuge, abortifacient, counter irritant, as paste in the treatment of ringworm and psoriasis, anti-fertility agents in males.
Seed juice	Bleeding piles and enlarged liver and spleen.
Root	Abortifacient, diuretic, checking irregular bleeding from the uterus, piles, anti-fungal activity.
Leaves	Young leaves as vegetable, jaundice (fine paste), urinary complaints & gonorrhoea (infusion), dressing wounds (fresh leaves), antibacterial activity, vermifuge, in colic, fever, beriberi, abortion (infusion), asthma (smoke).
Flowers	Jaundice, emmenagogue, febrifuge and pectoral properties.
Stem bark	Jaundice, anti-haemolytic activity, STD, sore teeth (inner bark), anti-fungal activity.

are several reports on the therapeutic properties and pharmacological actions of papaya based on modern scientific investigations. Some have been discussed below.

Antimicrobial

The seed of papaya has antimicrobial activity against *Trichomonas vaginalis* trophozoites. The report suggests the use of papaya seed in urinogenital disorder like trichomoniasis with care to avoid toxicity[23]. The seed and pulp of papaya was shown to be bacteriostatic against several enteropathogens such as *Bacillus subtilis, Enterobacter cloacae, Escherichia coli, Salmonella typhi, Staphylococcus aureus, Proteus vulgaris, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* by the agar cup plate method[24]. Purified extracts from ripe and unripe fruits also produces very significant antibacterial activity on *S. aureus, Bacillus cereus, E. coli, P. aeruginosa* and *Shigella flexneri*[25].

The aqueous extract of fruit exhibited antimicrobial activity and promoted significant wound healing in diabetic rats. The seeds of irrespective stage of fruit maturity have bacteriostatic activity on Gram positive and Gram negative organisms, which could be useful in treating chronic skin ulcers. The papaya seed macerate has a clinical potential on conjugal R plasmid transfer from *Salmonella typhimurium* to *Escherichia coli,* on *in vitro* and in the digestive tract of genotobiotic mice. Herbal formulations containing papaya leaves and root or leaves alone as one of the constituent has antibacterial activity against *Salmonella typhi, S. paratyphi* and *S. typhimurium*; however, water, acetone and ethanol extract of papaya leaves showed no microbicidal activity[26-30].

Anthelmintic

The air dried papaya seeds given as elixir with honey has shown significant effect on the human intestinal parasites, without significant side effects. It is reported that their consumption offers a cheap, natural, harmless, readily available monotherapy and preventive strategy against intestinal parasitosis, especially in tropical communities[31]. Preliminary pharmacological report on anthelmintic activity of papaya seed is also available. Benzylisothiocyanate, present in seeds is the chief or sole anthelmintic[19, 32-34].

The latex of papaya has anthelmintic efficacy against *Heligmosomoides polygyrus* in experimentally infected mice, which suggests its potential role as an anthelmintic against potent intestinal nematodes of mammalian hosts[35]. It also has anthelmintic activity against natural infection of *Ascaris suum* in pigs and found to be 100% effective at the dose of 8g/kg body weight[36]. The plant extracts of papaya possesses a dose dependent significant effect on the egg, infective larvae and adult worms of *Trichostrongylus colubriformis*[37]. Alcoholic extracts of papaya shows potential *in vitro* anti-parasitic action, which affects eggs, infective larvae and adult *Haemonchus contortus*[38].

Anti-amoebic

The cold macerated aqueous extract of matured papaya seeds has shown anti-amoebic activity against *Entamoeba histolytica*[39].

Antimalarial

The petroleum ether extract of the rind of raw papaya fruit exhibits significant antimalarial activity. There may be significant commercial potential in extracting the active element from this plant, which grows abundantly throughout the tropics and the rind of which is discarded as waste, can be exploited for antimalarial activity[40].

Antifungal

The latex of papaya and Fluconazole has synergistic action on the inhibition of *Candida albicans* growth. This synergistic effect results in partial cell wall degradation (as indicated by transmission electron microscopy observations)[41]. Latex alone is statically effective on *C. albicans* when added to a culture during the exponential growth phase and approximately 60% was achieved. This fungistatic effect is the result of cell wall degradation due to a lack of polysaccharides constituents in the outermost layers of the fungal cell wall and release of cell debris into the culture medium[42]. Latex proteins appear to be responsible for antifungal action and minimum protein concentration for producing a complete inhibition was reported as about 138mg/ml[43].

Effect on smooth muscles

Ethanol extract of papaya seeds at 0.1-6.4mg/ml showed concentration dependent inhibition of jejunal contractions and found significantly irreversible. Thus, seed extract is capable of weakening the contractile capability of isolated rabbit jejunum[44]. Pentane extract of papaya seeds has shown relaxation

action on strips of dog carotid artery that had been pre-contracted with Phenylephrine. At the higher concentration, these are reported to be cytotoxic due to increasing the membrane permeability to Ca^{2+} (Ref. 45). A crude ethanol extract of unripe fruit produces a significant depression of mean arterial pressure but the extract has about 28% more depression action than hydrallazine in the hypertensive rats. Fruit juice of papaya probably contains antihypertensive agent(s), which exhibits mainly alpha adenoreceptor activity [46,47]. Papaya leaves extracts exhibited more than 50% relaxing effect on aortic ring preparations. This property demonstrates that many edible plants common in Asian diets possess potential health benefits, affording protection at the vascular endothelium level[48].

Rat uterine contractile activity was remarkably increased by different doses of papaya latex extract in proestrus and estrus stages compared to metestrus and diestrus stages of the estrous cycles. Crude papaya latex contain a uterotonic principle which might be a combination of enzymes, alkaloids and other substances which can evoke sustained contraction of the uterus acting mainly on the alpha adrenergic receptor population of the uterus at different stages[49]. Ethanol extract (80%) of seeds causes a concentration dependent tocolysis of uterine strips isolated from gravid and non-gravid rats. High concentration extract is capable of causing irreversible uterine tocolysis probably due to the damaging effect of benzylisothiocyanate on the myometrium[50].

Diuretic

Aqueous root extract of papaya when given orally at a dose of 10 mg/kg to rats produces significant increase in urine output and shows similar profiles of urinary electrolyte excretion to that of Hydrochlorothiazide[51].

Hepatoprotective

The ethanol and aqueous extracts of the fruit possess remarkable hepatoprotective activity against CCl_4 induced hepatotoxicity. But hepatoprotective mechanism as well as active principles responsible for hepatoprotective activity of this plant is not yet known[52].

Topical use

Papaya fruits are used as topical ulcer dressings by registered nurses in the Spanish Town Hospital, Kingston Public Hospital and the University Hospital of the West Indies, Jamaica, which promotes desloughing, granulation and healing; it also reduces the odour in chronic skin ulcers. It is cost effective and is considered to be more effective than other topical applications in the treatment of chronic ulcers[53]. It is currently used in The Gambia at the Royal Victoria Hospital, Banjul in the Paediatric Unit as the major component of burns dressings, where it is well tolerated by the children. Economic and widely available, the pulp of the papaya fruit is mashed and applied daily to full thickness onto the infected burns. It appears to be effective in desloughing necrotic tissue, preventing burn wound infection and providing a granulating wound suitable for the application of a split thickness skin graft. Possible mechanisms of action include the activity of proteolytic enzymes chymopapain and papain, as well as an antimicrobial activity[54].

Male antifertility

Seed extract showed pronounced hypertrophy and hyperplasia of pituitary gonadotrophs. Whereas the male rats treated with seed extract revealed gradual degeneration of Germ, Sertoli and Leydig cells as well as germinal epithelium, which confirmed its antifertility activity[55]. Aqueous extract of papaya seeds, 3 weeks after commencement of administration showed that the lumina of the seminiferous tubules were more prominent and empty in the experimental animals with no evidence of spermatids and spermatozoa[56]. Verma *et al* have reported its effect on cauda epididymal microenvironment[57].

The benzene chromatographic fraction of the chloroform extract of the seeds possesses reversible male contraceptive potential and the effect appears to be mediated through the testis[58] and may be directly rendered on the spermatozoa[59] without adverse toxicity. Another study revealed inhibition of sperm motility due to other epididymal factors rather than the sub-cellular characteristics of testis and epididymis[60]. A possible mechanism of action and preliminary studies on the antifertility effect of crude seeds on the gonads of male albino rats has been done by Udoh and Kehinde[61]. A recent report revealed that it has good contraceptive efficacy in langur monkey and the action is mediated through inhibition of sperm motility[62].

The chloroform extract of seeds has shown contraceptive efficacy and reversibility in decreasing the sperm concentration in male adult rabbits. It

produces gradual decline in the sperm concentration, reached severe oligospermia (fewer than 20 million/ml) after 75 days treatment and attained uniform azoospermia after 120 days of treatment. It also affects the sperm motility and viability after 45 days of treatment and reached less than 1% after 75 days of treatment[63]. It may selectively act on the developing germ cells, possibly mediated via Sertoli cells, leading to azoospermia[64]. The crude chloroform extract of seed causes suppression of cauda epididymal sperm motility, which reduces fertility to zero % within 40 to 60 days of treatment[65]. Reversible sterility could be induced in male rats using seed's aqueous extract without adverse effects on libido and toxicological profile[66] and it could serve as an effective male contraceptive in rodents[67]. Even aqueous extract of papaya bark has potential contraceptive activity[68]. However, aqueous extract of the seeds of papaya failed to exhibit contraceptive effects at any of the dose regimens tested on male rabbits, contrary to the observations made in the previous studies. Unaltered toxicological profiles indicated that the drug was free of side effects[69].

Papaya seed extract changes the biochemical parameters (except cholesterol levels) and the contractile pattern of vas deferens. The distal vas deferens will affect more than the proximal vas and recovery will be slower probably due to its higher threshold requirement for androgen[70]. A short term administration of an aqueous extract of papaya seed manifests an androgen deprived effect on the target organs and thereby causes antifertility effect in adult male albino rats. The data revealed that functional sterility could be induced in male rats by papaya seed extract treatment, which promises to be a potential male contraceptive as also supported by its traditional use in different parts of Assam[71,72].

Female antifertility

Sharma and Mahanta have reported that the composite root extract containing papaya root extract as one of the constituent, induces morphological changes in the endometrial surface epithelium in albino rat uterus. The characteristic smooth regular pattern of normal epithelium appears to have changed at places by haphazardly oriented groups of cells and loss of microvilli indicating a disorganized picture[73]. Whereas seeds aqueous extract has shown abortifacient properties on female Sprague Dawley rats[74] and the petroleum ether, alcoholic and aqueous extracts inhibits ovulation in rabbits[75]. The papaya seed extracts did not exhibit anti-zygotic, anti-implantation, early abortifacient or antifertility activity[76].

Normal consumption of ripe papaya during pregnancy may not pose any significant danger. However, the unripe or semi-ripe papaya (which contains high concentration of the latex that produces marked uterine contractions) could be unsafe in pregnancy[77].

Histaminergic

Crude latex causes contraction of the isolated guinea pig ileum strips, which is mediated via H_1-receptor and dependent on extracellular Ca^{2+} influx[78]. Papaya flower pollen is able to induce respiratory IgE-mediated allergy. The existence of common allergens among papaya flower pollen, fruit and papain has been demonstrated by RAST inhibition[79].

Immunomodulatory

The involvement of oxidative stress mechanisms in several biological and pathological processes including ageing, cancer, cardiovascular and neurodegenerative diseases has continued to fuel suggestions that processes can potentially be modulated by treatment with free-radical scavengers and antioxidant. The fermented papaya preparation has shown its ability to modulate oxidative DNA damage due to H_2O_2 in rat pheochromocytoma cells and protection of brain oxidative damage in hypertensive rats[80]. It has also exhibited potential supportive role on oxidative inflammatory damage in cirrhosis caused by hepatitis C virus[81]. The safety and antioxidative stress potential of papaya juice is found to be comparable to the standard antioxidant compound α-tocopherol[82]. The preparation containing yeast fermented papaya as one of the constituent has antioxidant actions and that it may be prophylactic food against age related and neurological diseases associated with free radicals[83].

Bacteriostatic activity of papaya could be correlated to its scavenging action on superoxide and hydroxyl radicals, which could be part of the cellular metabolism of such enteropathogens[24]. Bio-catalyzer, which contains yeast fermented papaya, may be useful as health foods against neural lipid peroxidation, traumatic epilepsy and ageing[14]. Consumptions of guava and papaya fruits reduce oxidative stress and alter lipid profile. Thus, it could reduce the risk of disease caused by free radical activities and high cholesterol in blood[84].

Papaya seed extract is currently being marketed as a nutritional supplement with purported ability to rejuvenate the body condition and to increase energy. The product claims to improve immunity against common infection and body functioning. This provides the evidence for its immunomodulatory and anti-inflammatory actions[85].

Fermented papaya preparation exerts both immunomodulatory and antioxidant activity in the macrophage cell line RAW 264 and it is a macrophage activator, which augments nitric oxide synthesis and TNF-alpha secretion independently of lipopolysaccharides[86]. The antioxidant cocktail derived from fermentation of unpolished rice, papaya and seaweeds with effective microorganisms of lactic acid bacteria, yeast and photosynthetic bacteria has shown inhibition of lipid peroxidation *in vivo*, a point dependent on the concentrations of bioactive flavonoids[87].

Conclusion

Papaya, popularly known as food article is the unique source of various types of compounds having diverse structure. Quite a significant amount of work has been done on the biological activity and possible application of these compounds and hence extensive investigation on its pharmacodynamics, kinetics and proper standardization and clinical trials is needed to exploit their therapeutic utility to combat various diseases.

References

1. Jean Bruneton, *Carica papaya, In*: Pharmacognosy, Phytochemistry of Medicinal plants, 2nd Edn, Technique & Documentation, France, 1999, pp. 221-223.
2. Bhattacharjee SK, *Carica papaya, In*: Hand book of Medicinal Plants, 3rd Revised Edn, by Shashi Jain (Ed), Pointer publisher, Jaipur, 2001, pp.1-71.
3. The Wealth of India–A Dictionary Indian Raw Materials and Industrial Products: Raw Materials Series, Revised edn, Vol. 3 Ca-Ci, Publications & Information Directorate, CSIR, New Delhi, 1992, pp. 276-293.
4. Indian Materia Medica by K M Nadkarni, 1st Edn by A. K. Nadkarni, Popular Prakashan Pvt. Ltd, Bombay, 1954, pp.273-277.
5. Internet search, Jean Mendows, Sarasota herald, Tribune, Food Section, Sep 25, 1995, http,//sarasota.extension.ulf.edu/fcs/FFFindex.html, http,//www.bawarchi.com/health/index.html, http,//www.specialtyproducts.com.
6. Marotta F, Weksler M, Naito Y, Yoshida C, Yoshioka M and Marandola P, Nutraceutical supplementation, effect of a fermented papaya preparation on redox status and DNA damage in healthy elderly individuals and relationship with GSTM1 genotype, a randomized, placebo-controlled, cross-over study, *Ann N Y Acad Sci,* 2006, **1067**(1), 400-407.
7. Marotta F, Pavasuthipaisit K, Yoshida C, Albergati F and Marandola P, Relationship between aging and susceptibility of erythrocytes to oxidative damage, in view of nutraceutical interventions, *Rejuven Res,* 2006, **9**(2), 227-230.
8. Dominguez de Maria P, Sinisterra JV, Tsai SW and Alcantara AR, *Carica papaya* lipase (CPL), an emerging and versatile biocatalyst, *Biotechnol Adv*, 2006, **24**(5), 493-499.
9. Kamaruzzaman M, Chowdhury SD, Podder CK and Pramanik MA, Dried papaya skin as a dietary ingredient for broiler chickens, *Br Poult Sci,* 2005, **46**(3), 390-393.
10. Fouzder SK, Chowdhury SD, Howlider MA and Podder CK, Use of dried papaya skin in the diet of growing pullets, *Br Poult Sci,* 1999, **40**(1), 88-90.
11. Lans C, Harper T, Georges K and Bridgewater E, Medicinal plants used for dogs in Trinidad and Tobago, *Prev Vet Med,* 2000, **45**(3-4), 201-220.
12. Marotta F, Safran P, Tajiri H, Princess G, Anzulovic H, Ideo GM, Rouge A, Seal MG and Ideo G, Improvement of haemorheological abnormalities in alcoholics by an oral antioxidant, *Hepatogastroenterology,* 2001, **48**(38), 511-517.
13. Osanto JA, Korkina LG, Santiago LA and Afanas'ev IB, Effects of bio-normalizer (a food supplementation) on free radical production by human blood neutrophils, erythrocytes, and rat peritoneal macrophages, *Nutrition,* 1995, **11**(5), 568-572.
14. Santiago LA, Osato JA, Hiramatsu M, Edamatsu R and Mori A, Free radical scavenging action of Bio-catalyzer alpha.rho No.11 (Bio-normalyzer) and its by-product, *Free Radic Biol Med,* 1991, **11**(4), 379-383.
15. Ballot D, Baynes RD, Bothwell TH, Gillooly M, MacFarlane BJ, MacPhail AP, Lyons G, Derman DP, Bezwoda WR and Torrance JD, The effects of fruit juices and fruits on the absorption of iron from a rice meal, *Br J Nutr,* 1987, **57**(3), 331-343.
16. Savickiene N, Dagilyte A, Lukosius A and Zitkevicius V, Importance of biologically active components and plants in the prevention of complications of diabetes mellitus, *Medicina (Kaunas),* 2002, **38**(10), 970-975.
17. Chen YT, Hsu LH, Huang IP, Tsai TC, Lee GC and Shaw JF, Gene cloning and characterization of a novel recombinant antifungal chitinase from papaya (*Carica papaya*), *J Agric Food Chem,* 2007, **55**(3), 714-722.
18. Buttle DJ and Barrett AJ, Chymopapains, Chromatographic purification and immunological characterization, *Biochem J,* 1984, **223**(1), 81-88.
19. Kermanshai R, McCarry BE, Rosenfeld J, Summers PS, Weretilnyk EA and Sorger GJ, Benzyl isothiocyanate is the chief or sole

anthelmintic in papaya seed extracts, *Phytochemistry*, 2001, **57**(3), 427-435.

20. Stepek G, Buttle DJ, Duce IR, Lowe A and Behnke JM, Assessment of the anthelmintic effect of natural plant cysteine proteinases against the gastrointestinal nematode, *Heligmosomoides polygyrus, in vitro, Parasitology,* 2005, **130**(Pt 2), 203-211.

21. Indian Medicinal Plants by KR Kirtikar and BD Basu, Reprint, 2nd Edn, International Book Distributors, Dehra Dun, Vol. II, 1998, pp.1097-1099.

22. Arya Vaidya Sala, *Carica papaya, In*: Indian Medicinal Plants & Compendium of 500 species, 1st Edn, Vol I, Orient Longman Pvt Ltd, Hyderabad, 2005, pp. 383-384.

23. Calzada F, Yepez-Mulia L and Tapia-Contreras A, Effect of Mexican medicinal plant used to treat trichomoniasis on *Trichomonas vaginalis* trophozoites, *J Ethnopharmacol,* 2007, **113**(2), 248-251.

24. Osato JA, Santiago LA, Remo GM, Cuadra MS and Mori A, Antimicrobial and antioxidant activities of unripe papaya, *Life Sci*, 1993, **53**(17), 1383-1389.

25. Emeruwa AC, Antibacterial substance from *Carica papaya* fruit extract, *J Nat Prod*, 1982, **45**(2), 123-127.

26. Leite AA, Nardi RM, Nicoli JR, Chartone-Souza E and Nascimento AM, *Carica papaya* seed macerate as inhibitor of conjugative R plasmid transfer from *Salmonella typhimurium* to *Escherichia coli, in vitro* and in the digestive tract of genotobiotic mice, *J Gen Appl Microbiol,* 2005, **51** (1), 21-26.

27. Dawkins G, Hewitt H, Wint Y, Obiefuna PC and Wint B, Antibacterial effects of *Carica papaya* fruit on common wound organisms, *West Indian Med J,* 2003, **52**(4), 290-292.

28. Nayak SB, Pereira L Pinto and Maharaj D, Wound healing activity of *Carica papaya* Linn. in experimentally induced diabetic rats, *Indian J Exp Biol,* 2007, **45**(8), 739-743.

29. Nkuo-Akenji T, Ndip R, McThomas A and Fru EC, Anti Salmonella activity of medicinal plants from Cameroon, *Cent Afr J Med,* 2001, **47**(6), 155-158.

30. Regine Helena Silva dos Fernandes Vieira, Dalia dos Prazeres Rodrigues, Flavia Araujo Goncalves, Francisca Gleire Rodrigues de Menezes, Janisi Sales Aragao and Oscarina Viana Sousa, Microbicidal effect of medicinal plant extracts (*Psidium guajava* Linn. and *Carica papaya* Linn.) upon bacteria isolated from fish muscle and known to induce diarrhea in children, *Rev Inst Med Trop S Paulo,* 2001, **43**(3), 145-148.

31. Okeniyi JA, Ogunlesi TA, Oyelami OA and Adeyemi LA, Effectiveness of dried *Carica papaya* seeds against human intestinal parasitosis: a pilot study, *J Med Food,* 2007, **10**(1), 194-196.

32. Panse TB and Paranjpe AS, Isolation of carpasemine from papaya seeds, *Proc Indian Acad Sci,* 1943, **18** A, 140.

33. Krishnakumari MK and Majumder SK, Studies on anthelmintic activities of seeds of *Carica papaya* Linn., *Ann Biochem Exp Med,* 1960, **20**(1), 551-556.

34. Bose BC, Saifi AQ, Vijayvargiya R and Bhagwat AW, Pharmacological study of *Carica papaya* seeds with special reference to its anthelmintic action, Preliminary report, *Indian J Med Sci*, 1961, **15**(1), 888-892.

35. Satrija F, Nansen P, Murtini S and He S, Anthelmintic activity of papaya latex against *Heligmosomoides polygyrus* infections in mice, *J Ethnopharmacol,* 1995, **48**(3) 161-164.

36. Satrija F, Nansen P, Bjorn H, Murtini S and He S, Effect of papaya latex against *Ascaris suum* in naturally infected pigs, *J Helminthol*, 1994, **68**(4), 343-346.

37. Hounzangbe-Adote S, Fouraste I, Moutairou K and Hoste H, *In vitro* effects of four tropical plants on the activity and development of the parasitic nematode, *Trichostrongylus colubriformis, J Helminthol,* 2005, **79**(1), 29-33.

38. Hounzangbe-Adote MS, Paolini V, FourasteI, Moutairon K and Hoste H, *In vitro* effects of four tropical plants on three life-cycle stages of the parasitic nematode, *Haemonchus contortus, Res Vet Sci*, 2005, **78** (2), 155-160.

39. Tona L, Kambu K, Ngimbi N, Cimanga K and Vlietinck AJ, Antiamoebic and phytochemical screening of some Congolese medicinal plants, *J Ethnopharmacol,* 1998, **61**(1), 57-65.

40. Bhat Praveen G and Surolia Namita, *In vitro* Antimalarial activity of extracts of three plants used in the traditional medicine of India, *Am J Trop Med Hyg*, 2001, **65**(4), 304-308.

41. Giordani R, Gachon C, Moulin-Traffort J and Regli P, A synergistic effect of *Carica papaya* latex sap and fluconazole on *Candida albicans* growth, *Mycoses*, 1997, **40**(11-12), 429-437.

42. Giordani R, Cardenas ML, Moulin-Traffort J and Regli P, Fungicidal activity of latex sap from *Carica papaya* and Antifungal effect of D (+)-glucosamine on *Candida albicans* growth, *Mycoses,* 1996, **39**(3-4), 103-110.

43. Giordani R, Siepaio M, Moulin-Traffort J and Regli P, Antifungal action of *Carica papaya* latex, isolation of fungal cell wall hydrolyzing enzymes, *Mycoses,* 1991, **34**(11-12), 469-477.

44. Adebivi A and Adaikan PG, Modulation of jejunal contractions by extract of *Carica papaya* Linn. seeds, *Phytother Res,* 2005, **19**(7), 628-632.

45. Wilson RK, Kwan TK, Kwan CY and Sorger GJ, Effects of papaya seed extract and benzyl isothiocyanate on vascular contraction, *Life Sci,* 2002, **71**(5), 497-507.

46. Eno AE, Owo OI, Itam EH and Konya RS, Blood pressure depression by the fruit juice of *Carica papaya* Linn. in renal and DOCA-induced hypertension in the rat, *Phytother Res,* 2000, **14**(4), 235-239.

47. Abeywardena M, Runnie I, Nizar M, Suhaila M, Head R and Suhaila Momamed, Polyphenol-enriched extract of oil palm fronds

(*Elaeis guineensis*) promotes vascular relaxation via endothelium-dependent mechanisms, *Asian Pac J Clin Nutr*, 2002, **11**(7), 467-472.

48. Runnie I, Salleh MN, Mohamed S, Head RJ and Abeywardena MY, Vasorelaxation induced by common edible tropical plant extracts in isolated rat aorta and mesenteric vascular bed, *J Ethnopharmacol,* 2004, **92**(2-3), 311-316.

49. Cherian T, Effect of papaya latex extract on gravid and non-gravid rat uterine preparations *in-vitro, J Ethnopharmacol*, 2000, **70**(3), 205-212.

50. Adebivi A, Ganesan Adaikan P and Prasad RN, Tocolytic and toxic activity of papaya seed extract on isolated rat uterus, *Life Sci,* 2003, **74**(5), 581-592.

51. Bungorn Sripanidkulchai, Varima Wongpanich, Pisamai Laupattarakasem, Jamsai Suwansaksri and Dusit Jirakulsomchok, Diuretic effects of selected Thai indigenous medicinal plants in rats, *J Ethnopharmacol,* 2001, **75**(2-3), 185-190.

52. Rajkapoor B, Jayakar B, Kavimani S and Murugesh N, Effect of dried fruits of *Carica papaya* Linn. on hepatotoxicity, *Biol Pharm Bull,* 2002, **25**(12),1645-1646.

53. Hewitt H, Whittle S, Lopez S, Bailey E and Weaver S, Topical use of papaya in chronic skin ulcer therapy in Jamaica, *West Indian Med J,* 2002, **49**(1), 32-33.

54. Starley IF, Mohammed P, Schneider G and Bickler SW, The treatment of pediatrics burns using topical papaya, *Burns,* 1999, **25**(7), 636-639.

55. Udoh P, Essien I and Udoh F, Effects of *Carica papaya* (paw paw) seeds extract on the morphology of pituitary-gonadal axis of male Wistar rats, *Phytother Res,* 2005, **19**(12), 1065-1068.

56. Uche-N wachi EO, Ezeokoli DC, Adogwa AO and Offiah VN, Effect of water extract of *Carica papaya* seed on the germinal epithelium of the seminiferous tubules of Sprague-Dawley rats, *Kaibogaku Zasshi,* 2001,**76**(6), 517-521.

57. Verma RJ and Chinoy NJ, Effect of papaya seed extract on microenvironment of cauda epididymis, *Asian J Androl,* 2001, **3**(2), 143-146.

58. Lohiya NK, Mishra PK, Pathak N, Maniyannan B and Jain SC, Reversible azoospermia by oral administration of the benzene chromatographic fraction of the chloroform extract of the seeds of *Carica papaya* in rabbits, *Adv Contracept,* 1999, **15**(2), 141-161.

59. Pathak N, Mishra PK, Maniyannan B and Lohiya NK, Sterility due to inhibition of sperm motility by oral administration of benzene chromatographic fraction of the chloroform extract of the seeds of *Carica papaya* in rats, *Phytomedicine,* 2002, **7**(4), 325-333.

60. Maniyannan B, Mishra PK, Pathak N, Sriram S, Bhande SS, Panneerdoss S and Lohiya NK, Ultrastructural changes in the testis and epididymis of rats following treatment with the benzene chromatographic fraction of the chloroform extract of the seeds of *Carica papaya, Phytother Res,* 2004, **18**(4), 285-289.

61. Udoh P and Kehinde A, Studies on antifertility effect of paw paw seeds (*Carica papaya*) on the gonads of male albino rats, *Phytother Res,* 1999, **13**(3), 226-228.

62. Lohiya NK, Manivannan B, Goyal S and Ansari AS, Sperm motility inhibitory effect of the benzene chromatographic fraction of the chloroform extract of the seeds of *Carica papaya* in langur monkey, *Presbytis entellus entellus*, *Asian J Androl,* 2008 **10**(2), 298-306.

63. Lohiya NK, Mishra PK, Pathak N and Maniyannan B, Reversible contraception with chloroform extract of *Carica papaya* Linn. seeds in male rabbits, *Reprod Toxicol,* 1999, **13**(1), 59-66.

64. Lohiya NK, Mishra PK, Pathak N, Maniyannan B, Sriram S, Bhande SS and Panneerdoss S, Chloroform extract of *Carica papaya* seed induced long term reversible azoospermia in langur monkey, *Asian J Androl,* 2002, **4**(1), 17-26.

65. Lohiya NK and Goyal RB, Antifertility investigations on the crude chloroform extract of *Carica papaya* Linn. seeds in male albino rats, *Indian J Exp Biol,* 1994, **30**(11),1051-1055.

66. Lohiya NK, Goyal RB, Jayaprakash D, Ansari AS and Sharma S, Antifertility effects of aqueous extract of *Carica papaya* seeds in male rats, *Plants Med*, 1994, **60**(5), 400-404.

67. Chinoy NJ, D'Souza JM and Padman P, Effects of crude aqueous extract of *Carica papaya* seeds in male albino mice, *Reprod Toxicol,* 1994, **8**(1), 75-79.

68. Kusemiju O, Noronha C and Okanlawon A, The effect of crude extract of the bark of *Carica papaya* on the seminiferous tubules of male Sprague-Dawley rats, *Niger Postgrad Med J,* 2002, **9**(4), 205-209.

69. Lohiya Nirmal K, Pathak Neelam, Mishra Pradyumna K and Maniyannan B, Contraceptive evaluation and toxicological study of aqueous extract of the seeds of *Carica papaya* in male rabbits, *J Ethnopharmacol,* 2000, **70**(1), 17-27.

70. Chinoy NJ and Ranga Geetha M, Effects of *Carica papaya* seed extracts on the physiology of the vas deferens of albino rats, *Acta Eur Fertil,* 1984, **15**(1), 59-65.

71. Chinoy NJ and George SM, Induction of functional sterility in male rats by low dose *Carica papaya* seed extract treatment, *Acta Eur Fertil,* 1983, **14**(6), 425-432.

72. Tiwari KC, Majumdar R and Bhattacharjee S, Folklore information from Assam for family planning and birth control, *Int J Crude Drug Res*, 1982, **20**(3), 133-137.

73. Sharma HN and Mahanta HC, Modulation of morphological changes of endometrial surface epithelium by administration of composite root extract in albino rat, *Contraception,* 2000, **62**(1), 51-54.

74. Oderinde O, Noronha C, Oremosu A, Kusemiju T and Okanlawon OA, Abortifacient properties of aqueous extract of *Carica papaya* Linn. seeds on female Sprague-Dawley rats, *Niger Postgrad Med J,* 2002, **9**(2), 95-98.

75. Kapoor M, Garg SK and Mathur VS, Antiovulatory activity of five indigenous plants in rabbits, *Indian J Med Res,* 1974, **62**(8), 1225-1227.

76. Bodhankar SL, Garg SK and Mathur VS, Antifertility screening of plants. Part IX. Effect of five indigenous plants on early pregnancy in female albino rats, *Indian J Med Res,* 1974, **62**(6), 831-837.

77. Adebivi A, Adaikan PG and Prasad RN, Papaya (*Carica papaya*) consumption is unsafe in pregnancy, fact or fable? Scientific evaluation of a common belief in some parts of Asia using a rat model, *Br J Nutr,* 2002, **88**(2), 199-203.

78. Adebiyi A, Adaikan PG and Prasad RNV, Histaminergic effect of crude papaya latex on isolated guinea pig ileal strips, *Phytomedicine,* 2004, **11**(1), 65-70.

79. Blanco C, Ortega N, Castillo R, Alvarez M, Dumpierrez AG and Carrillo T, *Carica papaya* pollen allergy, *Ann Allergy Asthma Immunol,* 1998, **81**(2), 171-175.

80. Aruoma OI, Colognato R, Fontana I, Gartlon J, Migliore L, Koike K, Coecke S, Lamy E, Mersch-Sundermann V, Laurenza I, Benzi L, Yoshino F, Kobayashi K and Lee MC, Molecular effects of fermented papaya preparation on oxidative damage, MAP Kinase activation and modulation of the benzo[a]pyrene mediated genotoxicity, *Biofactor*, 1998, **26**(2), 147-159.

81. Marotta F, Yoshida C, Barreto R, Naito Y and Packer L, Oxidative-inflammatory damage in cirrhosis: effect of vitamin E and a fermented papaya preparation, *J Gastroenterol Hepatol,* 2007, **22**(5), 697-703.

82. Mehdipour S, Yasa N, Dehghan G, Khorasani R, Mohammadirad A, Rahimi R and Abdollahi M, Antioxidant potentials of Iranian *Carica papaya* juice *in-vitro* and *in-vivo* are comparable to alpha-tocopherol, *Phytother Res,* 2006, **20**(7), 591-594.

83. Imao K, Wang H, Komatsu M and Hiramatsu M, Free radical scavenging activity of fermented papaya preparation and its effect on lipid peroxide level and superoxide dismutase activity in iron-induced epileptic foci of rats, *Biochem Mol Biol Int,* 1998, **45**(1), 11-23.

84. Rahmat A, Abu Bakar MF, Faezah N and Hambali Z, The effects of consumption of guava (*Psidium guajava*) or papaya (*Carica papaya*) on total antioxidant and lipid profile in normal male youth, *Asia Pac J Clin Nutr,* 2004, **13**(Suppl), S106.

85. Mojica-Henshaw MP, Francisco AD, De Guzman F and Tingo XT, Possible Immunomudulatory actions of *Carica papaya* seed extract, *Clin Hemorheol Microcirc,* 2003, **29**(3-4), 219-229.

86. Rimbach G, Park YC, Guo Q, Moini H, Qureshi N, Saliou C, Takayama K, Virgili F and Packer L, Nitric oxide synthesis and TNF-alpha secretion in RAW 264.7 macrophages, mode of action of a fermented papaya preparation, *Life Sci,* 2000, **67**(6), 679-694.

87. Aruoma OI, Deiana M, Rosa A, Casu V, Piga R, Peccagnini S, Dessi MA, Ke B, Liang YF and Higa T, Assessment of the ability of the antioxidant cocktail-derived from fermentation of plants with effective microorganisms (EM-X) to modulate oxidative damage in the kidney and liver of rats *in vivo*, studies upon the profile of poly- and mono-unsaturated fatty acids. *Toxicol Lett,* 2002, **135**(3), 209-217.