

Papaya: A gifted nutraceutical plant - a critical review of recent human health research

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ABSTRACT

The plant kingdom is considered to be a repository of modern medicine, attributable to their rich source of bio-active molecules and secondary metabolites. It is indeed the Nutraceuticals that enhance immunity and ensure a healthier life because of their prophylactic and therapeutic values. Over centuries, papaya [Caricaceae; (*Carica papaya* Linn.)] is a renowned nutritious and medicinal plant. Each part of the papaya like root, stem, leaf, flower, fruit, seed, rinds, and latex has its own nutraceutical properties. It serves as food, cooking aid, and Ethnomedicine to prevent and treat wide-range of diseases and disorders. It has also been traditionally used as appetite enhancer, meat tenderizer, purgative, medicinal acne, abortifacient and vermifuge. Over decades, a series of scientific attempts were made to authenticate the nutraceutical properties of papaya. These studies validated that the papaya has antiplasmodial, antitrichochromal, antitrichomonal, antidengue, and anti-cancer activities. They have also exhibited that papaya possesses antiseptic, antiparasitic, anti-inflammatory, antidiabetic, and contraceptive features, and it helps in the management of sickle-cell anaemia, HIV, heart diseases and digestional disorders too. Nevertheless, the responsible bio-active molecules and their mode of actions remain indistinct and imprecise, and this calls for further pharmacological and clinical research on them. Conclusively, papaya is one of the naturally gifted plants; though its nutraceutical properties as a food or as a quasi-drug are poorly understood or undervalued by people. Accordingly, this scrutiny, demand for instigation of public health awareness campaigns to promote papaya consumption, so that the society shall acquire optimal benefits of papaya and in turn prevent and alleviate various diseases and illness.

Keywords *Carica papaya*, traditional system of medicine, nutraceutical, phytotherapy

INTRODUCTION

Infectious diseases are major public health issues in the resource-poor countries. They contribute to higher rate of morbidity and mortality related indices, due to fragile primary care settings and people's low socio-economic status to access the modern healthcare facilities. Despite recent scientific advancement and globalization, WHO estimates that in the developing countries, nearly 80% of the population remains to rely upon the traditional system of medicine (TSM) as a primary health care modality in the resource-constrained health care settings (Karunamoorthi et al., 2013a). Globally, since time immemorial, each and every society has had its unique way of indigenous health practice system in order to treat various ailments (Karunamoorthi, 2012a). TSM is one of the centuries-old practices and long-serving companions to the

human kind to fight against various diseases and to lead a healthy life. Every indigenous group has been using their unique approaches of TSM practice where among, the Chinese, Indian and African TSMs are world-wide renowned (Karunamoorthi et al., 2012).

In the near past, the generalization of modern health care services has posed immense threat to indigenous health practices due to their potential speedy therapeutic effect. However, even in the era of modern computational pharmacology approach, traditional medicinal plants serve as an important source and as a tool to treat various ailments in the developing countries (Karunamoorthi et al., 2012). The advent of most efficacious potent antimalarials such as chloroquine and artemisinin are products of our precious traditional knowledge of traditional medicinal plants. These recent successes inspire and encourage many researchers to investigate and validate the roles of traditional medicinal plants as phytotherapeutic agents (Karunamoorthi et al., 2013b).

Herbal medicinal system has been postulated and established through empirical observation and trial and error experiments since time immemorial to maintain good health and alleviate ailments and diseases (Karunamoorthi et al., 2013a). The Tamil traditional medicinal system, the so called Siddha system of medicine (SSM), which is an ancient indigenous practice the flourished and practiced for many

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Table 1. Definitions

	Definitions
Nutraceuticals	Any substance that is a food or a part of a food, which provides medical or health benefits, including the prevention and treatment of disease.
Phytochemicals	Bioactive non-nutrient plant compounds in fruits, vegetables, grains and other plant foods that have been linked in reducing the risk of major chronic diseases.
Traditional Medicine	WHO (2002) defines traditional medicine as including diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness.

centuries in Tamil Nadu, India, has the basic principle of the SSM as, “food itself is a medicine” which was postulated by the great 18 sages called Siddhars. The million-year old Siddha literature indicates that the plant-based therapeutic agents can cure many chronic diseases (Karunamoorthi et al., 2012).

The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ (Brower, 1998). According to DeFelice, nutraceutical can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease" (Brower, 1998). Nevertheless, the term nutraceutical as commonly used in marketing has no regulatory definition (Zeisel, 1999) (Table 1).

Since time immemorial, humankind has heavily relied upon plants as phyto-therapeutic agents to prevent/heal several ailments. However, in the modern era, the pharmaceutical industries have thrived by adopting modern scientific techniques and novel bio-technological tools, and developed several life-saving drugs, offering speedy recovery. Subsequently, the preventive as well as curative potency of nutraceutical plants are undervalued. In recent times, the health-conscious people have started realizing the chronic side-effects and persistent adverse health-hazards of conventional medicines. This has paved the healthy-way towards the unprecedented revived interest on nutraceutical plants. Nutraceuticals enhance immunity and ensure quality of life in terms of good health and longevity, providing a prophylactic approach.

Papaya is a major fruit crops known since ancient time, as nutritious and medicinal plant or herb (Table 2). It natives to southern Mexico and Central America nevertheless presently it is grown throughout the tropical regions of the world. The existing studies establish that the people are using papaya as a source of nutrition as well as phytotherapeutic agent by unique

Table 2. Taxonomy of *Carica papaya*

Taxonomy of <i>Carica papaya</i>	
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Brassicales
Family	Caricaceae
Genus	<i>Carica</i>
Species	<i>Papaya L.</i>

mode of preparation subsequently by consuming their parts. However, there is a paucity of data on efficacy and safety. In this perspective, this scrutiny is an effort to exemplify on the phytotherapeutic potentiality of papaya through data mining techniques from the prior scientific studies. It also delineates in relation to responsible active ingredients and their mode of action. In addition, it evaluates the existing challenges for future exploitation and development of affordable, accessible and safest papaya-based phytotherapeutic agents in the future.

Data mining and extraction

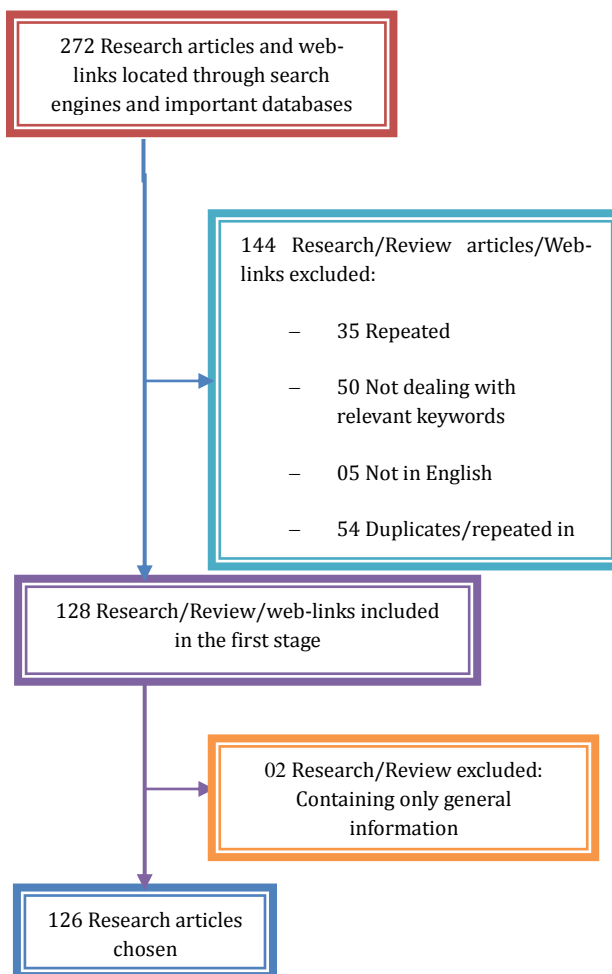


Fig. 1. The exclusion and inclusion criteria for choosing the appropriate research articles, notes and reviews for this narrative review.

Table 3. Vernacular name(s) of papaya in some of the important languages worldwide

NO.	Name of the Language	Vernacular Name(s)
1	Amharic	Papaya
2	Arabic	Fafay, Babaya
3	Bengali	Pspapaiva, Papeva
4	Burmese	Thimbaw
5	Creole	Papayer, Papaye
6	English	Bisexual pawpaw, Pawpaw tree, Melon tree, Papaya
7	Filipino	Papaya, Lapaya, Kapaya
8	French	Papailler, Papaye, Papayer
9	German	Papaya, Melonenbraum
10	Hindi	Papaya, Papeeta
11	Indonesian	Gedang, Papaya
12	Javaneses	Kates
13	Khmer	Ihong, Doeum lahong
14	Korean	파파야
15	Lao (Sino-Tibetan)	Houng
16	Luganda	Papaali
17	Malay	Papaya, Betek, Ketalah, Kepaya
18	Malayalam	Omakai
19	Marathi	Papai
20	Rajasthani	Eerankari
21	Sinhala	Pepol
22	Swahili	Mpapai
23	Tamil	Pappali, Pappayi
24	Telugu	Boppayi pandu
25	Thai	Ma kuai thet, Malakor, Loko
26	Tigrigna	Papayo
27	Vietnamese	Du du

Evidence acquisition

In order to collect appropriate research materials for the present scrutiny, a detailed search on Scopus, Medline, Google Scholar and Academic Search Premier Databases has been carried out for the time period 1950 - 2013. A Boolean search strategy was adopted and the keywords entered for search are “*Carica papaya*”, “Traditional medicine and papaya”, “Nutraceutical and papaya”, “Papaya as a phytotherapeutic agent” and “Papaya and diseases” in differing orders, in order to extract studies. The exclusion and inclusion criteria for choosing the appropriate research articles, notes and reviews were shown in Fig. 1 for this narrative review, and their bibliographic details (authors, title, full source, document type and addresses) were downloaded and maintained in a file.

Early history and distribution

The very earliest literary reference to papaya trees dates back to

1526, when they were found on the Caribbean coast of Panama and Colombia and described by the Spanish chronicler Oviedo. The history of papaya appears to be first documented by Oviedo, the Director of Mines in Hispaniola (Antilles) from 1513 to 1525, where he describes how Alphonso de Valverde took papaya seeds from the coasts of Panama to Darien, then to San Domingo and the other islands of the West Indies. The Spaniards coined it the name ‘papaya’ (Schery, 1952) (Table 3). However, there are some reports that describes that this plant has originated from the south of Mexico and Nicaragua (Chan and Paull, 2008), while others suggest that the origin is from the northwest of South America (Serrano and Cattaneo, 2010). However, after the discovery of the New World, the papaya tree has been spread widely throughout the tropics, most particularly in Africa and Asia. It is a very popular fruit, commonly cultivated and more or less naturalized in India, where it was introduced as early as 1598 (Schery, 1952).

Table 4. List of chemical constituents present in the various parts of papaya

NO.	Categories	Phytoconstituents	Plant Part(s)
1	Enzymes	Papain, chymopapain A and B, endopeptidase papain III and IV glutamine cyclotransferase, peptidase A and B and lysozymes.	Unripe fruit (Latex)
2	Carotenoids	β carotene, crytoxanthin, violaxanthin, zeaxanthin.	Fruits
3	Alkaloid & Enzyme	Carposide, and an enzyme myrosin.	Roots
4	Glucosinolates	Benzyl isothiocyanate, benzylthiourea, β -sitosterol, papaya oil, caricin and an enzyme myrosin.	Seeds
5	Minerals	Calcium, potassium, magnesium, iron, copper, zinc.	Shoots and Leaves
6	Monoterpenoids	4-terpineol, linalool, linalool oxide.	Fruits
7	Flavonoids	Quercetin, myricetin, kaempferol.	Shoots
8	Alkaloids	Carpinine, carpaine, pseudocarpine, vitamin C and E, choline, carposide.	Leaves and Heartwood
9	Vitamins	Thiamine, riboflavin, niacin, ascorbic acid, α -tocopherol.	Shoots and Leaves
10	Carbohydrates	Glucose, sucrose, and fructose.	Fruits

Ecology

Papaya is reported to tolerate annual precipitation of 6.4 to 42.9 dm (mean of 42 cases = 19.2), annual temperature of 16.2 to 26.6°C (mean of 42 cases = 24.5), and pH of 4.3 to 8.0 (mean of 33 cases = 6.1). Papaya is a tropical plant, killed by frost; does not tolerate shade, water logging, or strong winds, and may require irrigation in dry regions. It recuperates very slowly from serious root or leaf injury. It can be grown well below 1,500 m in well-drained, rich soil of pH 6 - 6.5 (Duke, 1983).

Morphological description

Papaya is a small, frost-tender, succulent, broadleaved evergreen tree that bears papaya fruits throughout the year. Each tree typically has a single, unbranched, non-woody trunk bearing the scars of old leaf bases. The trunk is topped by an umbrella-like canopy of palmately lobed leaves. Large, fleshy, melon-like fruits (papayas) hang in clusters attached to the trunk top just under the leaf canopy (Fig. 2). Papaya typically grows to 6 - 20' tall (container plants to 10' tall) and is most



Fig. 2. Papaya leaves arrangement like an umbrella-like canopy and melon-like unripe fruits hang in clusters attached to the trunk top just under the leaf canopy.

noted for its edible melon-like fruit. Papaya tree sometimes branches due to injury (Fig. 3) and it contains white latex in all parts. The stem is cylindrical, 10 - 30 cm in diameter, hollow with prominent leaf scars and spongy-fibrous tissue. It has an extensive rooting system (Orwa et al., 2009).

Leaves spirally arranged, clustered near apex of the trunk; petiole up to 1 m long, hollow, greenish or purplish-green (Fig. 4); lamina orbicular, 25 - 75 cm in diameter, palmate, deeply 7-lobed, glabrous, prominently veined; lobes deeply and broadly



Fig. 3. Papaya tree with branches



Fig. 4. Papaya unripe and semiripe fruits



Fig. 5. Papaya tree with flower and unripe fruits

toothed (Orwa et al., 2009). The species plants are typically dioecious (hermaphroditic), and maple trees are uncommon. Hermaphrodite trees (flowers with male and female parts) are the commercial standard, producing a pear shaped fruit. These plants are self-pollinated (Jari, 2009).

Flowers tiny, yellow, funnel-shaped, solitary or clustered in the leaf axils, of 3 types; female flowers 3 - 5 cm long, large functional pistil, no stamens, ovoid-shaped ovary; male flowers on long hanging panicles, with 10 stamens in 2 rows, gynoecium absent except for a pistillode; hermaphrodite flowers larger than males, 5-carpellate ovary; occurrence depends on the season or age of the tree (Orwa et al., 2009). The female flowers give way to smooth-skinned green fruits (Fig. 5) that ripen to yellow-orange with a yellow to pinkish-orange flesh and central cavity of pea-sized black seeds (Jari, 2009). However, several distinct varieties of papaya have been mentioned (Richharia, 1957; Sen, 1939), which vary in shape and size of fruits, height of plants, etc.

Description on papaya fruit

Papaya is melon-like fruit, round to oblong in shape and 3 to 5 inches in diameter (Figs. 5-6). The skin is smooth and thin,

shading from green in immature fruits to deep orange-yellow when ripe. The flesh, 1 to 2 inches thick, varies from pale yellow to a deep salmon-pink in color and a mildly sweet. The central cavity of the fruit contains many round black seeds (Fig. 7) (Low and Marezki, 1982). There are two main types of papayas produced: the small-sized Solo-type papayas (aka Hawaiian papayas), usually weighing between 1.1 and 2.2 pounds per unit, and the large-sized papayas (aka Mexican papayas), weighing up to 10.0 pounds per unit (EDI, 2012). The ripe papaya fruits are rich in vitamins, amino acids, calcium, iron, enzymes and so on (Tables 4 and 5). The protein in papaya is highly digestible. The fruit is usually consumed fresh but may be made into juice, pickles, preserves, jellies or sherbets or may be served cooked like cucurbits (Schery, 1952).

Chemical constituents

Papaya is considered one of the most important fruits because it is a rich source of antioxidant nutrients (e.g., carotenes, vitamin C, and flavonoids), the B vitamins (e.g., folate and pantothenic acid), minerals (e.g., potassium and magnesium), and fibre (EDI, 2012). Papaya plant is laticiferous as they contain specialized cells known as laticifers. The lactifiers secrete latex

Table 5. The phytomedicine contents of the 100 gm leaf, young fruit and ripe fruit of *C. papaya*

NO.	Name of the Phytonutrient	Papaya Plant Parts		
		Leaves	Unripe fruit	Ripe Fruit
1	Calories	79 cal	26 cal	46 cal
2	Vitamin A	18,250 SI	50 SI	365 SI
3	Vitamin B1	0.15 mg	0.02 mg	0.04 mg
4	Vitamin C	140mg	19 mg	78 mg
5	Calcium	353 mg	50 mg	23 mg
6	Hydrate Charcoal	11.9 gm	4.9 gm	12.2 gm
7	Phosphorus	0.0 gm	16 mg	12 mg
8	Iron	0.8 mg	0.4 mg	1.7 mg
9	Protein	8.0 gm	2.1 gm	0.5 mg
10	Water	75.4 gm	92.4 gm	86.7 gm



Fig. 6. The author with the unripen papaya fruit in Jimma zone, Eyihiopia



Fig. 7. Papaya fruit cavity containing black seeds

and are dispersed throughout most plant tissues. The papaya-latex is well known for being a rich source of the four cysteine endopeptidases namely papain, chymopapain, glycyI endopeptidase and caricain (Azarkan et al., 2003) and the content of latex may vary in fruit, leaves and roots. As the papaya fruit ripen, the amount of laticifers cells that produces latex decreases (OECD, 2005). Therefore, ripe papaya contains less latex and other constituents.

The richness of enzymes in papaya juice has been known since 1878 (Witmann, 1978). The most important enzyme papain was characterized in 1968 (Drenth et al., 1968). The enzymes chymopapain and papaya protease III were characterized in the 1980s of the last century (Jacquet et al., 1989; Zucker et al., 1985) These two important compounds like papain and chymopapain are supposed to aid in digestion and therefore they are widely used to cure the digestive disorders (Huet et al., 2006). In addition, papain is used in meat tenderizing, pharmaceuticals, beauty products, and cosmetics (EDI, 2012). Besides, it has been used in brewing and wine making, and in the textile and tanning industries. It is also used to treat arthritis.

It is important to note that the level and amount of the chemical compounds vary in the fruit, latex, leaves, and roots. The phytomedicine contents of the 100 gm of leaf, young fruit and ripe fruit of *C. papaya* are listed in Table 5. In addition, plant parts from male and female trees differ in the quantity of the compounds. For example, phenolic compounds tend to be higher in male trees than female trees. The amount of fresh papaya latex and dry latex (crude papain) also vary with the gender and age of the tree. Female and hermaphrodite trees yield cruder papain than the male trees and the older fruit yields more than the younger fruit. However, the activity of the papain is higher in the extracts from the younger fruit than the older fruit. Cultivars also vary in the quantity of the compounds (Cornel University, 2009). A recent study has reported that the green, yellow and brown leaves of papaya contain various phytochemicals, vitamins and minerals composition (Ayoola and Adeyeye, 2010). Therefore, the papaya leaves can be seen as a potential source of useful food and drug items.

Papaya as a nutraceutical: a healthy solution

The fruit is not just delicious and healthy, but the whole plant parts, fruit, roots, bark, peel, seeds and pulp are also known to have medicinal properties. Nutraceuticals enhance immunity

and ensure quality of life in terms of good health and longevity (Fig. 8). The many benefits of papaya owed due to high content of Vitamins A, B and C, proteolytic enzymes like papain and chymopapain which have antiviral, antifungal and antibacterial properties. The methanolic extract of the seeds and 2, 3, 4-trihydroxytoluene (caricaphenyl triol) (200 µg/ml) showed significant antifungal activity against *Aspergillus flavus*, *Candida albicans* and *Penicillium citrinium* (Singh and Ali, 2011).

C. papaya can be used for treatment of a numerous diseases like warts, corns, sinuses, eczema, cutaneous tubercles, glandular tumors, blood pressure, dyspepsia, constipation, amenorrhoea, general debility, expel worms and stimulate reproductive organs and many, and as a result *C. papaya* can be regarded as nutraceutical (Aravind et al., 2013). Papaya latex has been suggested for many diseases in different parts of the world (Warring, 1968). Chemopapain, a product of papaya, is commercially produced as a drug for sciatic pain. Papaya latex has been used as a vermifuge and has bacteriostatic effects on a number of infectious organisms. Another commercial product of papaya is papain, a proteolytic enzyme used to tenderize meat (Cherian, 2000).

Nutraceutical – nutrients/herbals that may prevent illness

Obviously, it has been well-known that the food cannot alleviate human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) infection, or treat the HIV virus, but it can positively improve the fitness and the quality of life. The malnourished people with HIV are sick more often than the nourished HIV infected individual and can develop AIDS furiously. The HIV infected/immune-compromised individuals are extremely vulnerable to opportunistic infections and these infection can be prevented by specialized nutritional supplement in terms of ingesting phytonutrient-rich fruits particularly papaya very regularly. Since papaya is a gifted nutraceutical plant, it offers an opportunity for controlling various diseases, particularly neurodegenerative diseases and in AIDS management (Bonuccelli, 2012). Recent studies indicate that the papaya may hold the cure to the deadly AIDS virus. Researchers in the Philippines believe that eating papaya could help in boosting the immune system and can reduce the viral load of HIV in some patients. Papaya juice is sometimes used in pharmaceuticals as it can be used to remove blemishes. Latex obtained from unripe fruits is used in folk medicine to treat

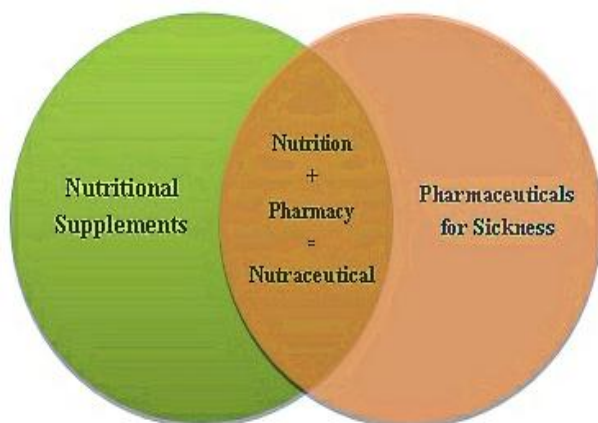


Fig. 8. Papaya a gifted Nutraceutical

warts and corns (Dass, 2010).

Fermented papaya preparation (FPP) (a product of yeast fermentation of *C. papaya*) is a food supplement. Studies in chronic and degenerative disease conditions (such as thalassaemia, cirrhosis, diabetes and aging) and performance sports show that FPP favourably modulates immunological, hematological, inflammatory, vascular and oxidative stress damage parameters. Neuroprotective potential evaluated in an Alzheimer's disease cell model showed that the toxicity of the β -amyloid can be significantly modulated by FPP. Oxidative stress-induced cell damage and inflammation are implicated in a variety of cancers, diabetes, arthritis, cardiovascular dysfunctions, neurodegenerative disorders (such as stroke, Alzheimer's disease, and Parkinson's disease), exercise physiology (including performance sports) and aging. These conditions could potentially benefit from functional nutraceutical/food supplements (as illustrated here with fermented papaya preparation) exhibiting anti-inflammatory, antioxidant, immunostimulatory (at the level of the mucus membrane) and induction of antioxidant enzymes (Aruoma et al., 2010). Papaya can be considered a medicinal food. Papain is the lauded enzyme derived from the papaya that is incorporated into several types of enzymatic health supplements. Although the evidence is scant, some sources even suggest that papain is helpful in fighting Hepatitis C.

Biological activities

Digestive system disorders

Papain extract is used as a treatment for certain intestinal and digestive problems. Ingredients of the papaya fruit and the processed fruit have been associated with a beneficial impact on digestion or diseases (Aruoma et al., 2010; Forstner, 1971; Ghoti et al., 2011; Marotta et al., 2011; Scolapio et al., 1999; Somanah et al., 2012). The fruit is considered as a traditional remedy for gastrointestinal functional disorders in countries with papaya plants. However, only little evidence has been produced with reference to its physiological effect in humans and the proof of efficacy. In line with these, Muss et al. (2013) studied the clinical effects of the papaya preparation called Caricol® in a double blind placebo controlled study design and found that the (Caricol®) contributes to the maintenance of digestive tract physiology. It ameliorates various functional disturbances, like constipation, heartburn, and symptoms of irritable bowel syndrome (IBS). Nevertheless, the mechanism of this digestive tract physiology support is discussed. The tea, prepared with the green papaya leaf, promotes digestion and

aids in the treatment of ailments such as chronic indigestion, overweight and obesity, arteriosclerosis, high blood pressure and weakening of the heart (Mantok, 2005).

Antiseptic agent

The fresh, green papaya leaf is an antiseptic, whilst the brown, dried papaya leaf is the best as a tonic and blood purifier (Bonsu, 1999). The green unripe papaya has a therapeutic value due to its antiseptic quality. It cleans the intestines from bacteria, (only a healthy intestine is able to absorb vitamin and minerals, especially vitamin B12) (Mantok, 2005). The yellow papaya leaf is equally used as anti-anaemic agent while the brown leaf is used as a body cleanser (Bonsu, 1999). Chewing the seeds of ripe pawpaw fruit also helps to clear nasal congestion (Kafaru, 1994).

Management of sickle cell anaemia

Folk medicine reportedly uses papaya as an herbal remedy for the management of sickle cell anaemia. The results indicate that the previously reported anti-sickling properties of papaya may be due to the inherent antioxidant nutrient composition, thus supporting the claims of the traditional healers and suggests a possible correlation between the chemical composition of the papaya plant and its uses in traditional medicine as an anti-sickle cell anemia agent (Imaga et al., 2010). In addition, Oduola et al. (2006) has described about the anti-sickling activity of unripe papaya extracts that the anti-sickling and reversal of sickling activities reside in the ethyl acetate fraction that prevents the sickling of hemoglobin of the sickle cell patients.

Anxiolytic and antioxidant activity

Papaya has been used in the Ethiopian traditional system of medicine to relieve stress and other disease conditions. Therefore a study was undertaken to evaluate the anxiolytic and sedative effects of 80% ethanolic papaya pulp extract in mice. The papaya pulp extract 100 mg/kg showed significant anxiolytic activity without altering locomotor and sedative effects and this study authenticated the traditional usage of papaya as an anxiolytic medicinal plant (Kebebew and Shibeshi, 2013). Similarly, a study was designed to explore the toxicological and antioxidant potential of dried *C. papaya* juice in vitro and in vivo. In vivo examination was performed after oral administration of dried papaya juice to rats for 2 weeks at doses of 100, 200 and 400 mg/kg. Blood TBARS and FRAP assays were used to determine the potential of the juice to act against oxidative stress. The acute toxicity test (LD_{50}) demonstrated that papaya juice is not lethal up to a dose of 1500 mg/kg after oral administration and thus is considered nontoxic. In treated groups, no sign of toxicity was observed. In vitro evaluation of the antioxidant effects of papaya showed that the highest antioxidant activity (80%) was observed with a concentration of 17.6 mg/mL. This preliminary study indicates the safety and antioxidative stress potential of the juice of papaya, which was found to be comparable to the standard antioxidant compound alpha-tocopherol (Mehdipour et al., 2006). The study conducted by da Silva et al. (2010) further supports the notion that papain, the compound isolated from the latex of unripe *C. papaya* is a promising source of potential antioxidant.

Management of heart diseases

Unripe pulp of *C. papaya* is rich in carbohydrate and starch (Oloyede, 2005) and also contains cardenolides and saponins that have medicinal value such as cardenolides used in the treatment of congestive heart failure (Schneider and Wolfing,

2004). Carpaine, an alkaloid with an intensely bitter taste and a strong depressant action on the heart, has been obtained mainly from the leaves, fruit and seeds of papaya (Hornick et al., 1978).

Anticancer agent

Papaya leaf juice is consumed for its purported anti-cancer activity by people living on the Gold Coast of Australia, with some anecdotes of successful cases being reported in various publications. Papaya leaf extracts have also been used for a long time as an aboriginal remedy for various disorders, including cancer and infectious diseases (Otsuki et al., 2010). There have been anecdotes of patients with advanced cancers achieving remission following consumption of tea extract made from papaya leaves. Papaya plants produce natural compounds (annonaceous acetogenins) in leaf, bark and twig tissues that possess both highly anti-tumor and pesticidal properties (McLanghlin et al., 1992). The papaya leaf tea or extract has a reputation as a tumour-destroying agent (Last, 2008).

To examine the potential role of papaya in anti-cancer therapy a study was conducted to exhibit the anti-tumour activity of the aqueous extract of the leaves of the papaya against various cancer cell lines, as well as its potential immunomodulatory effects, and attempted to identify the active components and observed significant growth inhibitory activity of the papaya extract on tumor cell lines. Finally, the identified active components of papaya extract are observed to inhibit tumour cell growth and to stimulate anti-tumour effects (Otsuki et al., 2010). In the leaves of papaya, components previously reported to potentially have anti-tumour activity includes tocopherol (Ching and Mohamed, 2001), lycopene (van Breemen and Pajkovic, 2008), flavonoid (Miean and Mohamed, 2001), and enzyliisothiocyanate (Basu and Haldar, 2008). A recent review conducted by Nguyen et al. (2013) indicated that to date no clinical or animal cancer studies were identified and only seven in vitro cell-culture-based studies were reported; these indicate that *C. papaya* extracts may alter the growth of several types of cancer cell lines. Nevertheless, many studies focused on specific compounds in papaya and reported bioactivity including anticancer effects. This review summarizes the results of extract-based or specific compound-based investigations and emphasizes the aspects that warrant future research to explore the bioactives in *C. papaya* for their anticancer activities. These studies clearly suggest that the papaya has a direct antitumor effect on various types of cancers, and therefore, it could be useful in possible therapeutic strategies in the fight against cancers.

Anthelmintic activity of papaya latex

In many of the resource-poor settings people could not afford to procure the commercially available modern anthelmintic agents (Gyuatt and Evans, 1992). As a result, one should not neglect the fact that there is a long tradition of using medicinal plants, some of which have been claimed, on empirical grounds, to possess anthelmintic activities (Dharma, 1985; Perry, 1980). One of the plants claimed to be effective against roundworms in humans is the papaya tree. In Papaya-producing countries the fruit is used as the drug for the treatment of parasitosis (Steppek, 1999) and infected skin lesions (Starley, 1999).

Papaya seeds are used against intestinal parasites in humans and farm animals in India (Lal et al., 1976), Central and South America (Roig and Mesa, 1974) and elsewhere (Werner, 1992). The extracts have been proven to be effective against *Caenorhabditis elegans* and other helminths in vitro and, where tested, in infected animals (Dar, 1965; Kermanshahi, 2001; Krishnakumari and Majumder, 1960; Robinson, 1958). Papaya latex has showed marked in vivo efficacy against the rodent

gastrointestinal nematode, *Heligmosomoides polygyrus* (Steppek, 1999).

In a recent experimental study, latex collected from young papaya fruits were shown to possess anthelmintic activity against patent *Ascaridia galli* infections in chickens (Mursof and He, 1991). A study was conducted to evaluate the possible anthelmintic activity of papaya latex against *Heligmosoraoides polygyrus* in experimentally infected mice. The results suggest a potential role of papaya latex as an anthelmintic against patent intestinal nematodes of mammalian hosts (Satrija et al., 1995).

Antitrichomonal activity

Trichomonas vaginalis causative agent of trichomoniasis is a flagellate protozoan that parasitizes the human vagina, prostate gland, and urethra. This parasitic infection has been associated with vaginitis, cervicitis, urethritis, prostatitis, epididymitis, cervical cancer, infertility, and pelvic inflammatory disease. The most significant clinical signs of trichomoniasis are vaginal or urethral discharge, foul-smelling discharge, dysuria, pruritus, severe irritation, abdominal pain, and edema or erythema. In pregnant women, trichomonads are implicated in premature membrane rupture, premature labor, and in the delivery of low-birth weight babies. In addition, *T. vaginalis* could have an important role in the transmission and acquisition of human immunodeficiency virus (Mundodi et al., 2009; Schwebke and Burgess, 2004; Swygard et al., 2004).

In order to improve the current chemotherapy of *T. vaginalis* infection, medicinal plants could be a source of new anti-protozoal drugs with high activity, low toxicity and lower price. Crude methanolic extracts from 22 Mexican medicinal plants were screened for anti-trichomonal activity against *T. vaginalis*. Among the plants tested *C. papaya* and *Cocos nucifera* showed the best anti-trichomonal activity with IC₅₀ values of 5.6 and 5.8 g/ml, respectively (Calzada et al., 2009).

Anti-dengue fever activity

Dengue fever is also known as breakbone fever and it is one of the great infectious scourges of mankind. It is caused by any one of four related viruses (Flaviviridae) and is transmitted through the infective bite of the mosquitoes, *Aedes aegypti* and *Aedes albopictus*. In the recent decades, it has become a major international public health concern. It has been estimated that over 2.5 billion (40%) of the world's population are at the risk of dengue infection. The WHO estimates that there may be 50-100 million cases worldwide every year. Before 1970, only nine countries had experienced severe dengue epidemics. However, now it is endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific region. Hence, it clearly shows that dengue is emerging and resurging as a global public health threat in a new changing environment, which is a matter of grave concern, calling for the innovative tools as well as approaches in terms of vector control, surveillance, and dengue fever case management. Dengue fever is mainly combated by a combination of vector control, personal protection and disease management by drugs. However, at the moment there are no specific antibiotics as well as potential reliable vaccine against dengue virus (DENV). Therefore, identifying affordable effective anti-dengue agent in terms of anti-dengue drugs is extremely important and inevitable too.

Recent reports have claimed possible beneficial effects of *C. papaya* leaf juice in treating patients with dengue viral infections. As a result, a study was conducted Ranasinghe et al. (2012) to evaluate the membrane stabilization potential of papaya leaf extracts using an in vitro hemolytic assay. Two

milliliters of blood from healthy volunteers and patients with serologically confirmed current dengue infection were freshly collected and used in the assays. Fresh papaya leaves at three different maturity stages (immature, partly matured, and matured) were cleaned with distilled water, crushed, and the juice was extracted with 10 ml of cold distilled water. Membrane stabilization properties were investigated with heat-induced and hypotonicity-induced hemolysis assays. Extracts of papaya leaves of all three maturity levels showed a significant reduction in heat-induced hemolysis compared to controls ($p < 0.05$). Papaya leaf extracts of all three maturity levels showed more than 25% inhibition at a concentration of 37.5 $\mu\text{g/ml}$ in vitro and could have a potential therapeutic effect on dengue disease processes causing destabilization of biological membranes.

In Pakistan a study was conducted by Ahmad et al. (2011) to investigate the efficacy of *C. papaya* leaves extracts against Dengue Fever Virus (DFV) in a 45 year old patient. The 25 ml of aqueous extract was administered daily, twice i.e. morning and evening for five consecutive days. Prior to the extract administration the patients' blood samples were analyzed for Platelets count (PLT), White Blood Cells (WBC) and Neutrophils (NEUT). Subsequently, following the administration the blood samples were again re-examined and found that there were significant rising of PLT, WBC and NEUT. The blood sample analysis clearly demonstrates that the aqueous extract of *C. papaya* leaves has the strong potential activity against DFV. It is important to note that this is a preliminary investigation and it needed further investigations for the isolation and identification of responsible bio-active molecules and their mode of action to combat dengue fever as well as various other viral diseases very effectively in the future.

Antiplasmodial activity

It has been estimated that nearly half of the world's population is at the risk of contracting malaria with sub-Saharan Africa being the most risky area (Karunamoorthi, 2014). Malaria is often referred to as a disease of poverty and a cause of poverty. It is quite understandable that malaria is quite endemic in nature in the poorest regions of the world (Karunamoorthi, 2012b). It imposes an enormous burden in terms of morbidity and mortality in the tropical and subtropical regions of the world, particularly Asian and sub-Saharan African countries. Quite often the main victims are expectant mothers and children under the age of five (Karunamoorthi et al., 2010a). Besides, it is one of the major obstacle to socioeconomic development as the main disease transmission seasons coincide with peak agricultural and harvesting period (Karunamoorthi and Bekele, 2009).

The existing malaria control intervention largely depends on the front-line arsenals like effective case management with artemisinin combination therapies (ACTs), distribution of long lasting insecticide treated nets (LLINs) and selective intradomicillary spraying (Karunamoorthi and Sabesan, 2013). However, global-warming concomitant effects, insecticide resistance, and drug resistance have fueled the resurgence and resurgence of many vector-borne diseases, particularly malaria (Karunamoorthi et al., 2010b; Karunamoorthi 2012c). Consequently, current malaria control is facing serious challenges to address the above cited issues by identifying the alternative plant-based affordable, accessible potential antimalarials (Karunamoorthi et al., 2013b), and in exploring the risk-reduced pesticides or green pesticides to combat malaria effectively (Karunamoorthi, 2012d). Since malaria is a major public health issue in the resource-limited settings, where there is a fragile health care system, it quite often fails to meet

the expectation of needy poor people. The existing potent antimalarial ACTs has been often unaffordable, inaccessible and the recent reports indicate the emergence of multi-drug resistance strains against ACTs too (Karunamoorthi and Tsehaye, et al., 2012). As a result, in order to address the antimalarial drug resistance catastrophe, a keen interest has been observed among the researches towards TSM to explore the possibilities of identifying the new affordable, accessible and potential antimalarial drugs from our age-old TSM.

Mature leaves of *C. papaya* are widely used to treat malaria and splenomegaly while the fruit is often used against anaemia, which can also be caused by malaria (Adjanohoun, 1996). The petroleum ether extract of the seed rind of this species showed a considerable antimalarial activity, with an IC_{50} of 15.19 $\mu\text{g/ml}$ (Bhat and Surolia, 2001). This clearly indicates that the papaya seeds contain the highly active antiplasmodial compounds. Moreover, Ngenyenya et al. (2004) has also recorded the antiplasmodial activity of the leaves and seeds of *C. papaya* with IC_{50} of about 60 $\mu\text{g/ml}$. In Ethiopia, Karunamoorthi and Tsehaye (2012) reported that the local residents are consuming the powder of the papaya seeds by mixing with honey orally as an antimalarial agent. A study was carried out evaluate the antimalarial activity of the methanolic seed extract of *C. papaya* on *Plasmodium berghei* infected mice. The seed extract of *C. papaya* showed a significant malaria parasitaemia suppressive activity ($p \leq 0.05$). These activities are dose dependent and comparable to those of Chloroquine phosphate. The present finding justifies the inclusion of the seeds of *C. papaya* in the treatment of malaria by local herbalists. The seeds extract therefore, if well purified and characterized may be used in treatment of very early plasmodiasis as well as a good prophylactic drug in human. This work is limited to animals, thus clinical trials in humans are recommended particularly, when *C. papaya* seeds are non-harmful/non toxic (Amazu et al., 2009).

Melariri et al. (2011) investigated the antiplasmodial properties of crude extracts from *C. papaya* leaves to trace the activity through bioassay guided fractionation. This study demonstrated greater antiplasmodial activity of the crude ethyl acetate extract of *C. papaya* leaves with an IC_{50} of 2.96/0.14 $\mu\text{g/ml}$ when compared to the activity of the fractions and isolated compounds. Yet the presence of alkaloids in the leaves of papaya could be the rationale why it is often being effectively administered as an anti-malarial agent (Ayoola and Adeyeye, 2010). However, so far there is no comprehensive report on the phyto-chemistry and mode of action of papaya with reference to its antiplasmodial activity. Therefore, further pharmacological and phytochemical investigations on papaya are required to be warranted to authenticate the claims or beliefs on the efficacy and safety concerns (Karunamoorthi and Tsehaye et al., 2012).

Insecticidal agent

Vector control is a corner stone in the fight against vector-borne diseases particularly malaria (Karunamoorthi, 2011). Insecticides are considered to be a powerful weapon in order to enhance the agricultural productivity and considerably to improve the major public health indices too (Karunamoorthi et al., 2012b). However, over the past six decades, insecticides are playing the crucial role to contain the vector-borne diseases and have saved hundreds of millions of lives every year. In the last decade, we have attained a remarkable success to combat with many arthropod-borne diseases particularly malaria. All credits go to the combined effect of IRS, long-lasting insecticidal nets (LLINs), and effective case management. However, now malaria vector control is facing a serious challenge in terms of

insecticide resistance, particularly against pyrethroids (Karunamoorthi and Sabesan, 2009).

Pyrethroid resistance is a potential threat to the global public health concern. It is largely due to the heavy reliance, recurrent and inappropriate pyrethroid usage. Therefore, it has to be addressed immediately to sustain the recent success of vector control, unless it would become uncertain (Karunamoorthi and Sabesan, 2013). It calls for the searching of new insecticides with novel mode of action. As a result, it is the hour to launch an extensive search to explore eco-friendly biological materials for the control of insect pests, and we are all just around the corner to reinstate the ubiquitous chemical of concern by plant-based products in the insect control (Karunamoorthi et al., 2008).

Over the centuries, even before the advent of modern synthetic pesticides our ancestors completely depended upon the usage of plant-derived products as a pesticidal agent against various insects. At the moment, a renewed interest has been observed to exploit the insecticidal control potentialities of various plant-based products (Karunamoorthi et al., 2009). The rationale behind the reawakened desire for searching the new plant-based insecticides with novel mode of actions is not only a part of new Integrated Pest Management (IPM) strategy, but it also inhibits the development of resistance with the existing chemical insecticides. It shall further reduce the heavy reliance of chemical pesticides as well as their adverse impact on human health and environment. In general, green pesticides/risk reduced pesticides are target-specific and can be non-toxic (Karunamoorthi, 2012d).

An investigation has been conducted to determine the mosquito-larvicidal potential of ten Nigerian plant crude extracts against the fourth instar larvae of *Anopheles gambiae*. The larvicidal activity (LA) expressed as % LA was concentration and incubation-time dependent. The out of ten plants at 5% w/v (12 and 24 h), only *C. papaya* and *Dacryodes edulis* have demonstrated remarkable larvicidal activity of 40% and 55% and 50% and 70%, respectively while the rest were largely inactive. This investigation suggests a potential use of papaya in the control of malaria vector mosquitoes (Oladimeji et al., 2012). The methanolic leaf extract of *C. papaya* showed lethal effects against the first- to fourth- instar larvae and pupae of *Culex quinquefasciatus*, the LC₅₀ value of I instar was 51.76 ppm, 2nd instar was 61.87 ppm, III instar was 74.07 ppm, and IV instar was 82.18 ppm, and pupae was 440.65 ppm, respectively (Kovendan et al., 2011).

Crude and solvent extracts of seed extract of *C. papaya* was investigated for anti-mosquito potential, including larvicidal, pupicidal and adulticidal, activities against *Cx. quinquefasciatus* and *An. stephensi*, the vector of filariasis and malaria, respectively. The mortality rate of 3rd larval instars of *Cx. quinquefasciatus* and *An. stephensi* at 0.5% concentration was significantly higher (*P* value - 0.05) than the mortality rates at 0.1%, 0.2%, 0.3% and 0.4% concentrations of crude extract. Among the solvent extracts, the petroleum ether extract showed the highest mortality at 100 ppm with LC₅₀ and LC₉₀ values of 31.16 ppm and 341.86 ppm against *Cx. quinquefasciatus*; 18.39 ppm and 250.76 ppm against *An. stephensi*. Papaya plant extract exhibited a slightly pupicidal potency with LC₅₀ values of 86.53 ppm and 72.16 ppm against *Cx. quinquefasciatus* and *An. stephensi* respectively (Rawani et al., 2012).

Mosquito repellent activity

Repellents are playing the pivotal role whenever and wherever other personal protection measures like ITNs are impossible or impracticable (Karunamoorthi and Sabesan, 2010). Plants have

been used since ancient times to repel/kill blood-sucking insects in the human history and even today, in many parts of the world people are using plant substances for the same (Karunamoorthi et al., 2008). Globally, numerous studies evidently suggest that the traditionally used plant-based insect repellents are promising and could potentially contain vectors of the disease (Karunamoorthi et al., 2014). This appropriate strategy affords for the opportunity to minimize chemical repellents usage and the risks associated with the adverse side effects (Karunamoorthi et al., 2010b). Water extracts of *C. papaya* seeds repel various kinds of insects. The extracts obtained by pressing the papaya roots destroy the nematodes in soil and the extracts from the immature fruit controls termites effectively (Buhner, 2000).

Crude and solvent extracts of seed extract of *Carica papaya* was investigated for adulticidal, smoke toxicity and repellent activities against *Cx. quinquefasciatus* and *An. stephensi*. It showed repellency against the adult females of both mosquito species with 78% and 92% protection respectively. It also provided biting protection time of 4 h and 5 h respectively against *Cx. quinquefasciatus* and *An. stephensi*. In adulticidal activity there is 70% and 63.3% death of adult mosquito against *Cx. quinquefasciatus* and *An. stephensi* after 72 h. The smoke toxicity test showed that out of 200 adult mosquitoes, 190 adult mosquitoes of *Cx. quinquefasciatus* and 186 mosquitoes of *An. stephensi* dropped down at the floor after 5 h of smoke (Rawani et al., 2012).

A study was conducted to document the efficacies of mosquito repellents from extracts of plants such as *Capsicum frutescens*, *C. papaya* and *Cyanodon dactylon*, which are traditionally known to repel mosquitoes. The results suggesting that the distillates of the fruits of *C. frutescens* and *C. papaya* were effective for 2.5 h, whilst the mixture of *C. frutescens* and *C. papaya* was effective for 4 h. Whereas the mixture of *C. papaya* and *C. dactylon* was effective for 2.5 h. Mixtures of highly repellent extracts are observed to offer higher protection against *Aedes aegypti* mosquitoes (Kazembe and Makusha, 2012). It is well-known that to-date, the scientific community has tested over thousands of traditional repellents plants to identify the potential plant-based insects/mosquitoes repellents. These findings clearly suggesting that papaya extracts possess remarkable larvicidal, pupicidal, adulticidal and repellent activity against various species of vector mosquitoes. However, further investigations are required to be warranted to elucidate the responsible bio-active ingredients and their mode of mechanism in the near future. There are many key challenges and issues that lie ahead for the advancement of the ideal commercial insect repellent from plant as a source (Karunamoorthi, 2012e).

Genito-urinary infection

Dried and pulverized leaves are used for making tea; also the leaf decoction is administered as a purgative for horses and used for the treatment of genito-urinary system (Adebisi et al., 2002).

The contraceptive efficacy and reversibility

The oral administration of an aqueous suspension of the powder of papaya seeds induces sterility in 40% of treated male rats, without affecting the weight of the genital organs, spermatogenesis, and the motility of the spermatozoa (Das, 1980). Chinoy et al. (1984) reported a complete loss of fertility in albino rats and mice treated with aqueous extract of the seeds of *C. papaya* i.m. at 0.5 mg and 5 mg/kg body wt./d for 7 d. The papaya seed extract induce variable degree of responses depending on dose, duration, and route of administration in

laboratory animals. In rabbits, dry seed powder of papaya suspended in distilled water and administered orally resulted in complete sterility in rats (Vyas and Jacob, 1984). Among the various extracts tested, it was reported that the chloroform extract and partially purified fractions of the chloroform extract were more effective in male rats (Lohiya and Goyal, 1992; Lohiya et al., 1994a, b). The effects were reversible and without appreciable changes in the toxicological profile.

An extensive investigation is being carried out in various animal models with various extracts of the seeds of papaya, to evaluate as a potential male contraceptive tool (Lohiya et al., 1999). The contraceptive efficacy and reversibility of the chloroform extract of the seeds of papaya in adult male rabbits were investigated. Sperm concentration showed a gradual decline, reached severe oligospermia (fewer than 20 million/ml) after 75 d treatment, and attained uniform azoospermia after 120 d treatment. Sperm motility and viability were severely affected after 45 d treatment and reached less than 1% after 75 d treatment. The morphology of the spermatozoa by scanning electron microscopy revealed membrane damage in the acrosome, bent midpiece, coiled tail, and detached head and tail. Histology of the testis revealed arrest of spermatogenesis beyond the level of spermatocytes. No toxicity was evident from the haematology and serum biochemistry parameters. The libido of the treated animals was unaffected and the fertility rate was zero. The effects were comparable in both the dose regimens (Groups II and III) and were restored to normal 45 d after withdrawal of the treatment (Lohiya et al., 1999).

Goyal et al. (2010) conducted a study to authenticate scientific documentation of the seeds of papaya being traditionally used for contraception and to establish safety of the methanol sub-fraction (MSF) of the seeds of papaya as a male contraceptive following long term oral treatment. They found that the long term daily oral administration of MSF affects sperm parameters without adverse side effects and is clinically safe as a male contraceptive. The seeds of papaya are reported to possess emmenagogue, abortifacient and antifertility properties (Chopra et al., 1958).

In trials with rats, daily oral doses of benzene and alcohol extracts (20 mg/kg body weight (BW) for 30 days) did not affect body or reproductive organ weights or adversely affect liver or kidney function. However, aqueous extracts (1 mg/kg BW for 7 or 15 days) and benzene extracts given orally to female rats caused infertility and irregular oestrous cycles. Male rats given ethanol seed extracts orally (10 or 50 mg/day for 30, 60, or 90 days) or intramuscularly (0.1 or 1.0 mg/day for 15 or 30 days) had decreased sperm motility. The oral doses also decreased testis mass and sperm count. Studies with aqueous seed extracts also decreased fertility in male rats. The fertility of the male and female rats returned to normal within 60 days after the treatments were discontinued (Cornel University, 2009). In addition to decreasing infertility, papain might cause abortions shortly after conception. The papain apparently dissolves a protein(s) responsible for adhering the newly fertilized egg to the wall of the uterus (Cornel University, 2009).

Traditional uses of papaya

Papaya fruits, seeds, latex and extracts have been used traditionally to treat various ailments in humans across the world. According to the folk medicine, papaya latex can cure dyspepsia and also applicable for external burns and scalds. Seeds and fruits are excellent anti-amoebic (Okeniyi et al., 2007). Dried and pulverized leaves are sold for making tea; also the leaf decoction is administered as a purgative for horses and used for the treatment of genetic-urinary system (Adebiyi

et al., 2002). Papain is popularly used as a chewing gum additive and beer clarifier plus for a large number of additional medical, cosmetic and industrial purposes.

Carapine, an alkaloid present in papaya, can be used as a heart depressant, amoebicide and diuretic. The fruit and juice are eaten for gastrointestinal ailments; a fresh leaf poultice is used to treat sores. The fresh root with sugarcane alcohol can be taken orally or as a massage to soothe rheumatism. A flower decoction is taken orally for coughs, bronchitis, asthma and chest colds. In some countries, the seeds are used as an abortifacient and vermifuge (Orwa et al., 2009). Leaves have been poulticed into nervous pains, elephantoid growths and it has been smoked for asthma relief among tropical tribal communities. The stem and bark may be used in rope production (Rawani et al., 2012).

Wound healing properties

Wound healing, or wound repair, is the body's natural process of regenerating dermal and epidermal tissue. The sequence of events that repairs the damage is categorized into separate inflammatory, proliferative and maturation phases (Diegelmann and Evans, 2004). Extracts from the epicarp of green papaya used in this experiment have been shown to be beneficial for treatment of wounds. This finding is consistent with the observation that topical application of the unripe fruit papaya promotes desloughing, granulation and healing and reduced odor in chronic skin ulcers (Hewitt et al., 2000). Recent study conducted by Anuar et al. (2008) also has confirmed about the ripe fruits improves wound healing property. Topical treatment of mush pulp of papaya containing papain and chymopapain for pediatric infected burns was effective for desloughing necrotic tissue, preventing infection and roviding a granulating wound (Starley, 1999).

Meat tenderizer and other uses

Green papayas are sometimes cooked as a vegetable; they also can be pickled or candied. Papain, the protein-splitting enzyme found in green papaya, is extracted and sold commercially as a meat tenderizing sauce. This tenderizing effect can also be achieved by laying slices of green papaya or green papaya skin on the meat and allowing it to stand for several hours (Low and Marezki, 1982). Milky juice of unripe fruits is used as a cosmetic to remove freckles and other blemishes from the skin. The seeds have a mild, peppery taste and may be ground and used in place of pepper in salad dressings or in recipes calling for, mustard seed. If eaten in large quantities may cause diarrhea due to the presence of the benzylisothiocyanate (BITC) in papaya seeds (Low and Marezki, 1982). The seeds are also used as emmenagogue, thirst quenchers, carminatives or for bites and stings of poisonous insects (Wiat, 2006). The papaya has been traditionally used to treat several skin diseases. In Cambodia, Laos and Vietnam, latex is used to treat eczema and psoriasis (Amenta et al., 2000).

Toxicological profile

Papaya leaves have been used in ethnomedicine for the treatment of various diseases and illness. Despite its benefits, very few studies on their potential toxicity have been described. A study was carried out to characterize the chemical composition of the leaf extract from 'Sekaki' *C. papaya* cultivar by UPLC-TripleTOF-ESI-MS and to investigate the sub-acute oral toxicity in Sprague Dawley rats at doses of 0.01, 0.14 and 2 g/kg by examining the general behavior, clinical signs, hematological parameters, serum biochemistry and histopathology changes. A total of twelve compounds consisting of one piperidine alkaloid, two organic acids, six

malic acid derivatives, and four flavonol glycosides were characterized or tentatively identified in the *C. papaya* leaf extract. In the sub-acute study, the *C. papaya* extract did not cause mortality nor were treatment-related changes in body weight, food intake, water level, and hematological parameters observed between treatment and control groups. Histopathological examination of all organs including liver did not reveal morphological alteration. Other parameters showed non-significant differences between treatment and control groups. The results suggest that *C. papaya* leaf extract at a dose up to fourteen times the levels employed in practical use in traditional medicine in Malaysia could be considered safe as a medicinal agent (Afzan et al., 2012).

Papaya seed preparations are used in traditional medicine to expel intestinal worms in human and ruminants. In the study, an ethanol extract of papaya seeds (EEPS; 0.1 - 6.4 mg/ml) caused concentration-dependent inhibition of jejunal contractions in contrast to corresponding concentrations of DMSO (solvent control). The inhibitory effect of EEPS on jejunal contractions was significantly irreversible. Previous studies have indicated that benzyl isothiocyanate (BITC) is the main bioactive compound responsible for the anthelmintic activity of papaya seeds. In the present study, standard BITC (0.01 - 0.64 mmol/l) also caused significant irreversible inhibition of jejunal contractions. Cryosections of the jejunum showed marked morphological damage of the segments treated with BITC in contrast to DMSO-treated segments. EEPS-induced jejunal damage was, however, less marked. These results indicate that papaya seed extract and BITC, its principal bioactive constituent are capable of weakening the contractile capability of rabbit isolated jejunum. It is thus envisaged that at the toxic level that will be needed to kill and expel intestinal worms *in vivo*, BITC may also cause impairment of intestinal functions (Adebiyi and Adaikan, 2005).

A study was conducted to investigate the acute toxicity of papaya leaf extract on Sprague Dawley rats at a dose of 2000 mg/kg body weight (BW). Sighting study was conducted in a stepwise procedure using the fixed doses of 5, 50, 300, and 2000 mg/kg. The single oral dose of the papaya leaf extract did not produce mortality or significant changes in the body weight, food and water consumption. The relative weights of the internal organs were normal. However, hemoglobin (HGB), hematocrit (HCT), red blood cell (RBC) and total protein were significantly increase indicating dehydration. Apart from triglyceride, other biochemistry parameters demonstrated no significant changes as compared to the control. (Halim et al., 2011). Melissa et al. (2008) reported that the male and female Wistar rats ($N = 56$) received diets containing transgenic or non-transgenic papayas at twice the equivalent of the average daily human consumption of fresh papayas. No adverse effects on animal behaviour or differences in body weight and organ weight between control and treated groups were observed during the study. Necropsy at the end of the study indicated that neither pathological nor histopathological abnormalities were present in the liver and kidneys of rats in the control and treated groups. The present scrutiny clearly found that the exception of infertility, the literature reviewed did not indicate any adverse reactions from the consumption of papaya fruit, latex, or extracts. However, the leaves and roots of papaya contain cyanogenic glucosides which form cyanide. The leaves also contain tannins. Both of these compounds, at high concentrations, can cause adverse reactions. Also, inhaling papaya powder (high in the enzymes papain and chymopapain), can induce allergies (Cornel University, 2009).

Consuming papaya fruit is it safe during pregnancy?

In fact, this is one of the foremost questions around the world people keep on questioning to obtain an accurate answer due to some of the popular belief in many countries. Through this scrutiny, the author would like to convey to the people bit cautiously by citing a few earlier scientific reports that the consumption of ripe papaya fruits during pregnancy causes no risk. However, the ingestion of unripe and semi-ripe papaya could be unsafe during pregnancy (Adebiyi et al., 2002). It induces miscarriage in susceptible pregnant women. It is purely the unripe fruit contains much more latex compared to the ripe papaya. Adaikan and Adebiyi (2004) found that crude papaya latex contains papain and chymopapain. They are strong uterine contractants and cause uncontrolled uterine contractions leading to abortion (Cherian, 2000).

CONCLUSIONS

Indeed, papaya is an ancient herbal medicinal plant. It is nutritious and medicinal values well-known worldwide. In the ethnomedicine it has been used as a nutraceutical to treat/prevent wide range of diseases/disorders, including cancer. Besides, it also has traditionally been used for various purposes like meat tenderizer, contraception, medicine acne, menstrual pain reducer, and appetite enhancer. The findings of the present scrutiny clearly suggest that the papaya plant parts possess powerful anti-plasmodial, anti-trichochromal, anti-trichomonal, anti-dengue, and anti-cancer properties. It also exhibits its potentiality as antiseptic, anti-parasitic, anti-inflammatory, anti-diabetic, contraceptive activity, and management of sickle cell anemia and heart diseases, indigestions and dysfunctions in the gastrointestinal tract. However, the modes of actions are not clearly understood, therefore further clinical studies have to be undertaken to delineate about the mechanisms.

This scrutiny also clearly suggests papaya as one of the excellent Nutraceutical Plants. Therefore enormous public health awareness campaigns must be instigated through printed and electronic media about the new linking of food and optimal health. Furthermore, the policy makers, physicians, public health experts and nutriounist must advocate the optimal benefits of papaya as a food or as a quasi drug to prevent/treat various ailments through social media. Besides, currently the conservation and sustainable utilization of edible plant and their biodiversity for the food production and nutraceutical is a matter of grave concern. Therefore, appropriate precautionary measures must be taken for the preservation and cultivation of papaya tree as it is an excellent choice in terms of socio-economic perspective. The author hopes that it could be extremely helpful for the further enhancement of traditional system of medicine in the developing world too.

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CONFLICT OF INTEREST

None to declare.

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