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Review Article

Importance of Bioactive Compounds Present in Papaya (*Carica papaya*) Seed Flour in Human Health

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Abstract

Papaya (*Carica papaya*) is a species of the Caricaceae family. It is a perennial tropical tree that is widely cultivated, producing fruits that are consumed throughout the world. All of its parts can be used: stem, leaves, flowers, fruit and seeds. Fruit processing generates considerable amounts of waste. Disposal of these materials is often a problem, in addition to legal restrictions. For this reason, new technologies must be developed to take advantage of these plant residues. The use of papaya seeds is part of the by-products whose technological applications and nutritional potential are still Little known by the agri-food sector. One of the characteristics is that they do not contain toxic compounds or gluten, and they are also rich in bioactive compounds, protein, crude fat, fatty acids, carotenoids, total phenolic compounds and fiber. Regarding health, the seeds are used to treat intestinal worms, ulcers, sickle cell anemia and poisoning. As well as an antibacterial and anti- inflammatory effect on the digestive system. Therefore, it is concluded that papaya seed flour is a good alternative for use in the fortification of agri-food products with an impact on human health.

Keywords: Papaya; Seed; Seed Flour; Human Health; Bioactive Compounds

Introduction

Growing concerns about human health have led to a demand for functional foods, as consumers recognize the significant link between food and well-being by seeking foods that not only satisfy hunger and provide essential nutrients, but also help protect against disease and promote overall health [1]. Literally thousands of phytochemicals present in fruits, flowers, leaves, stems and roots of plants have been found to be safe and widely effective alternatives with fewer adverse effects during consumption to treat a disease [2]. The addition and/or fortification of these nutritional compounds in processed and unprocessed Food products help in the daily diet by creating or improving new formulations such as: breads, jams, jellies, cakes, juices, pastries, dairy products among others, and nutritionally enriched foods, providing fiber, protein, essential fats, vitamins, minerals and antioxidants [3]. Agricultural and agro-industrial activities generate a huge amount of waste and quality by-products, of which a high percentage is incorporated into rivers and lakes, while others are burned or incorporated into the soil as fertilizer, causing environmental pollution. Therefore, as possible uses of waste and residues are discovered and applied, they can acquire added value and benefit the economy [4]. Papaya (*Carica papaya*) is a species of the *Caricaceae* family, it is a perennial, woody, fast-growing tropical tree up to 10 m tall, short-lived and with self-supporting stems which is widely cultivated producing a fruit that is consumed throughout the world [5]. During papaya processing, the peel, seeds and damaged parts can constitute more than 50 % of the fruit, which generates environmental contamination problems [6,7]. The abundant availability throughout the year and lower economic value of papaya seeds have encouraged nutritionists to exploit this by-product as a food ingredient rich in anti-

oxidants, as well as a functional food for humans and animals [8]. Studies conducted on hypoglycemic and hypolipidemic effects and other diseases, the aqueous extract of papaya seed flour has been shown to progressively reduce fasting blood glucose concentration, triglycerides, total cholesterol, LDL cholesterol (low-density lipoprotein) and VLDL cholesterol, and increase HDL cholesterol (high density lipoprotein) [7].

Characteristics of papaya (*Carica papaya*)

Papaya (*Carica papaya*) is one of the most important fruits belonging to the *Caricaceae* family, with more than 22 species. Only one member of the Carica genus is cultivated as a fruit tree [9,10]. It is a dicotyledonous plant that reproduces dioeciously or gynodiaceously [11]. Papaya tree is a perennial, woody, fast-growing, short-lived plant up to 10 m tall with self-supporting stems, it usually grows as a single-stemmed plant but can become multi-stemmed when damaged [12]. Several species of *Caricaceae* are used as medicine in a wide variety of diseases [13-16]. It is a fruit cultivated in tropical and subtropical regions of the world [6,7,15,18,19]. More than 13 million tons are produced annually in India, Brazil, Indonesia, Nigeria, Mexico and other countries ([7,18,20,21]. All parts of the papaya plant can be used as medicine, the fruit pulp, flowers, and seeds [13,14,22]. It is low in calories and loaded with phytochemicals that help maintain human health [10,16] Its skin is thin and covers the edible pulp, it is orange to red in color and surrounds a central cavity filled with small black seeds [10,23]. According to the Food and Agriculture Organization of the United Nations (FAO), it is an invaluable plant that is prevalent throughout the world. The benefits of papaya and its components are due to its high content of vitamin A, B and C, proteolytic enzymes such as papain and chymopapain, minerals and antioxidants that have antiviral, antifungal and antibacterial properties [19].

Agro-industrial waste

Over the last decade, awareness about environmental conservation and sustainability of natural resources has been growing [24]. As a result, these efforts are gaining importance worldwide. Fruit sector industries generate highly perishable bio-waste that leads to the dumping of solid waste and environmental pollution, producing gases, pathogenic microorganisms, high oxygen demand, soil and water contamination, among others [10,16,17,19,23-25]. Fruit processing generates considerable amounts of waste, such as peels, roots, leaves, flowers and seeds. The disposal of these materials is often a problem, coupled with legal restrictions. For this reason, new technologies must be developed to take advantage of these plant residues for use in production as food additives or supplements with high nutritional value; their recovery can be economically attractive [10,17,26]. Waste products such as fruit seeds, which contain polyphenolic compounds and have significant antioxidant capacity and economic value, are not being used [19] as is the case of *C. papaya* fruits, which generate peels and seeds [23], which constitute around 50% of the fruit [6,7].

Importance of papaya seeds (*Carica papaya*)

Papaya seeds are tiny black spheres covered with a gelatinous aril; however, this can vary depending on the species, they represent about 16 to 20 % of the weight of the fresh fruit and are considered a waste by-product [8,21,24,27]. The abundant availability throughout the year and lower economic value of the seeds has encouraged nutritionists to exploit this by-product as an ingredient in protein rich foods as well as a functional food in humans and animals [28]. Furthermore, they do not contain toxic compounds or gluten, making them a safe ingredient for diets [27,28]. Another functional characteristic is the wáter retention capacity, which is highly desirable in the meat industry as an additional ingredient to enrich some products [7]. The use of papaya seeds is part of the by-products whose technological applications and nutritional potential are still Little known by the agri-food sector [18]. In some countries such as China, India, Indonesia and Brazil, they are not considered waste since they contain many valuable bioactive compounds such as crude protein, crude fat, fatty acids (oleic acid (71.30 %), followed by palmitic acid (16.16 %), linoleic acid (6.06 %) and stearic acid (4.73 %)). The predominant tocopherols are α and δ-tocopherol, with 51.85 and 18.9 mg kg^{-1}, respectively. They also contain carotenoids such as β- cryptoxanthin (4.29 mg kg^{-1}) and β-carotene (2.76 mg kg^{-1}) and total phenolic compounds of 957.60 mg kg^{-1} [7,15,22,28]., crude fiber, carpaine, caricin, oil, glucotropacoline and an enzyme myrosin, alkaloids, tannins, phenols, saponins, ethyl acetate and n-butanol fractions, benzyl isothiocyanate, benzylthiourea, glucotropacoline, benzylglucosinolate, hentriacontane, β-sistosterol and flavonoids, which may serve as antimicrobials, immunomodulators, gastrointestinal anthelmintics and antioxidants [3,9,16,29,30]. Papain and other endopeptidases

present in both papaya fruits and seeds have been used for medical purposes in Central America for decades, such as wound defibrination and edema treatment [9,30]. Research into the potential, extraction and preservation of bioactive compounds from fruit seeds (grape, cocoa, tuna, mango, papaya) has identified some problems, polyphenolics are susceptible to factors such as temperature, oxygen, light, pH and enzymes. However, there are various methods to preserve these biocompounds, such as microencapsulation by spray drying, a technique that offers advantages such as short production times, temperature control and operational [19]. The seeds of *C. papaya* are becoming more popular due to their therapeutic properties. It can be eaten and has a pungent, pungent taste. It is occasionally powdered and used as an alternative to black pepper [21].

Papaya seed flour (*Carica papaya*)

Papaya seed flour contains about 26 % lipids, 25 % proteins and 29 % fibers, minerals such as calcium, iron, magnesium, manganese, potassium, phosphorus, copper and zinc, it is rich in oil content, which mainly consists of monounsaturated fatty acids and nutraceuticals, such as oleic, palmitic, linolenic and stearic acid, tocopherols such as α- and δ-tocopherol, and β-cryptoxanthin carpaine, benzyl isothiocyanate, benzyl glucosinolate, glucotropacoline, benzylthiourea, hentriacontane, β-sitostrol, caricin and myrosin enzyme, in addition, alkaloids, flavonoids, tannins, saponins, anthraquinones [7,9,16,27,28,31], it has been used in the manufacture of bakery products, pastas, jams, sausages, and other products, increasing the content of fiber, protein, carbohydrates, vitamins, oils, minerals and flavonoids [6,7,10,16]. This by-product is rich in phytochemicals, particularly phenolic compounds, known for their antioxidant properties. In particular, they offer various nutritional and health benefits due to their nutritional richness. Extracts from some fruit seeds have become popular in recent years and attempts to characterize their bioactive principles have gained momentum for various pharmaceutical and Food processing applications [2]. Studies have indicated that papaya flour extracts possess anticancer, hypolipidemic, antifertility and anti-inflammatory properties [26].

Antimicrobial effect of papaya seed (*Carica papaya*)

Infectious diseases are the biggest threat to human health, with more tan 50,000 deaths occurring daily worldwide. Plants have the main advantage of being a more effective and cheaper pharmacological alternative [16,19]. The resistance of several infectious agents to synthetic drugs may be the main reason for the development of alternatives to antibiotics. The fruit, seeds, leaves and peels of Carica papaya have been shown to exert an antimicrobial effect on these potentially dangerous microorganisms. Papaya seed extract was observed to exert antimicrobial activity against Trichomonas vaginalis, although caution is advised when using the extract for urogenital disorders due to its toxicity [9]. Aqueous and ethanolic seed powders and extracts have been shown to reduce infection by phytopathogenic fungi and bacteria such as: *Botrytris cinerea*, *Penicillium digitatum*, *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella flexneri* and *Rhizopus stolonifer* that cause many deaths [9,17,25]. Studies have shown that it is effective in killing or inhibiting *E. coli*, *Salmonella*, *Staphylococcus*, and other bacterial infections of concern to health. There are even reports that it has been successfully used in viral infections such as dengue [27]. Traditionally, it can be used for the treatment of roundworms (*Ascaris lumbricoides*), indigestion, diarrhea, skin diseases, colds, male contraceptives (Masfufatun and Putri, 2019) [14,22,30]. These same authors determined the MIC (Minimum Inhibitory Concentration) of papaya seed ethanol extract to inhibit the growth of *Candida albicans* and *Vibrio cholerae* and analyzed its active compounds, concluding that the extract has high antimicrobial activity against *V. cholerae* and low antimicrobial activity against *C. albicans*. Papaya seeds are believed to have a strong antibacterial and anti-inflammatory effect on the digestive system [27].

Human health impact of papaya (*Carica papaya*) seed flour

Noncommunicable diseases (NCDs) kill 41 million people each year, accounting for 71% of deaths worldwide. Metabolic risk factors contribute to four key metabolic changes that increase the risk of NCDs: increased blood pressure, overweight and obesity, hyperglycemia and hyperlipidemia, all caused by excessive consumption of highly processed foods [10,15,31]. Advances in health sciences,

especially nutrition, demonstrate that the catastrophic and growing risk and mortality from these diseases can be reduced with an adequate intake of fruits and vegetables due to their excellent nutritional and functional properties, which are directly linked to physiological and metabolic processes in humans [6]. Growing human health problems could be exacerbated by the adverse effects of seemingly harmless foods and condiments that outperform existing medicines [10,22]. Synthetic antioxidants can have negative effects on humans and animals, making it necessary to increase the search for natural antioxidants of plant origin that can enhance the effect of reactive oxygen species [22]. Functional foods are similar in appearance to conventional foods, the former is consumed as part of the normal diet, while functional foods are foods that have a potentially positive effect on health beyond basic nutrition, have also demonstrated physiological benefits and can reduce the risk of chronic diseases [14,27]. Papaya and its components are revered by naturopathic physicians in most countries because all parts of the plant have various medicinal properties. The leaves and stem have bioactive compounds that inhibit metabolic processes in tumor cells. Extracts of the leaves are used as an antiseptic, blood tonic for the treatment of constipation, obesity, high blood pressure, and cardiac disorders. Extracts of the ripe fruit are used as remedies against malaria and hypertension. However, these are harmful to pregnant women because of their abortifacient and teratogenic properties. Extracts of unripe fruits are medicines for ulcers, diabetes, and sickle cell anemia. Commercially, papain, a proteolytic enzyme from unripe papaya, is used in industries to clarify beer, tenderize meat, and make medicines for digestive disorders. The seeds are used to treat intestinal worms, ulcers, sickle cell anemia and poisoning [11,32,33]. Papaya seeds are believed to have strong antibacterial and anti-inflammatory effect on digestive system [27]. As a medicinal plant, papaya seeds, fruits and leaves have been widely used in China as a remedy because it can protect liver and stomach from disharmony due to its antibacterial, anti-inflammatory, antiparasitic, antimutagenic, wound healing, nephroprotective, antiamoebic, antiulcer, antidiabetic, antiobesity, anticancer and antiaging properties, and can scavenge oxidative radicals such as $^{\cdot}OH$, O_2 and H_2O_2 [9,16,17,31] *Carica papaya* seed extracts have been observed to exert anti-diabetic effects in studies conducted on laboratory animals, it has also been linked to the treatment of poison-related kidney disorders, as well as an anti-male fertility effect in male rats, rabbits, and monkeys. Therefore, it could be used for the pharmaceutical development of a male contraceptive as studies have shown that it inhibits sperm motility in humans and animals [34]. These same authors evaluated the effect of *Carica papaya* seed oil on the lipid and antioxidant profile in the brain, plasma and erythrocytes of albino rats, concluding that the consumption of this oil in large quantities increases the concentrations of reduced glutathione in erythrocytes, making the oil a good source of antioxidants [11,21]. Papaya seed extracts may be a sustainable candidate for deworming of school-aged children [35,36]. If confirmed by further studies, papaya seed-fortified school food could act as an alternative or complement to current mass deworming programs targeting school children [35,37]. It has also shown anticancer activity in HL-60 acute promyelocytic leukemia cells at an IC 50 of 20 µg/mL. A study conducted on the hypoglycemic and hypolipidemic effects of *Carica papaya* seed aqueous extract investigated in normal male rats showed that it progressively reduced fasting blood glucose, triglycerides, total cholesterol, LDL (low-density lipoprotein) cholesterol, and VLDL cholesterol, and increased HDL (high-density lipoprotein) cholesterol [20,28,38]. Mesquita., *et al*. [21] evaluated the nutritional and bioactive potential of papaya seeds (var. Formosa) at different stages of ripening, in addition to studying the seed oil and hydroethanolic seed extracts, they concluded that the hydroethanolic extract obtained from the seeds is rich in phenolic compounds and is suitable for use in foods as an antioxidant.

Utilization of papaya (*Carica papaya*) flour in food products

Large amounts of waste are generated as a result of industrial papaya processing, which aims to produce a range of products, such as candied fruits, raisins, nectars, jellies, juices, jams, papain and pectin. Many studies have already evaluated different ways of extracting oil from papaya seeds [20]. Bakery products, particularly cakes, are widely consumed worldwide and are preferred by both younger and older populations in both urban and rural areas. Cakes are typically composed of ingredients such as flour, fat, and the fat content of cakes contributes significantly to caloric intake. Food fortification involves enriching foods with specific nutrients such as proteins, minerals, and vitamins from plant sources. These fortified foods are particularly beneficial for people with malnutrition or specific health conditions [1]. Piovesan., *et al*. [37] found that incorporation of papaya seed extract into chicken sausages reduced lipid oxidation compared to the control group. Furthermore, papaya seed extract showed potential to reduce oxidation in

vegetable oils and foods. Kugo., *et al*. [35], they included ground papaya seeds in daily school meals combined with maize flour, a common ingredient for school nutrition in Africa, and concluded in this study that enriching a common school porridge with *Carica papaya* sedes significantly reduces the burden of *Ascaris lumbricoides* infection. Mérida., *et al*. [10] compared wheat flour with papaya seed flour and showed that it contains a higher amount of nutrients compared to wheat flour. Protein and fiber influence the functional properties analyzed since they improve the water retention capacity. However, it is not suitable to use this composite flour in food products where the incorporation of air is required in its formulation, such as ice cream and confectionery, although it is possible to use it in battered or fried foods since, the higher the percentage of flour used, the lower the oil absorption when frying. They used treatments with 5 and 10% substitution of papaya seed flour and these behaved very similar to the control treatment in the results of textura properties. The authors demonstrated that with these percentages they can be used in the preparation of certain bakery products such as boxed bread, muffins or donuts, providing a high concentration of fiber and protein and a low percentage of carbohydrates.

Conclusions

Papaya seeds (*Carica papaya*) are considered as agro-industrial waste, which can be a source of environmental pollution, however, processing them as flour and incorporating it as a raw material to agro-food products gives added value to this by-product, in addition to incorporating nutrients such as lipids, proteins, fibers, minerals such as calcium, iron, magnesium, manganese, potassium, phosphorus, copper and zinc, it is rich in oil content (monounsaturated fatty acids and nutraceuticals, such as oleic, palmitic, linolenic and stearic acid), tocopherols such as α- and δ-tocopherol, and β-cryptoxanthin carpaine, benzyl isothiocyanate, benzyl glucosinolate, glucotropacoline, benzylthiourea, hentriacontane, β-sitostrol, caricin and myrosin enzyme, in addition, alkaloids, flavonoids, tannins, saponins, anthraquinones. These compounds, according to the cited bibliography, favor human health in the antibacterial, antiparasitic, antimutagenic, healing, nephroprotective, antiamoebic, antiulcer, antidiabetic, antiobesity, cancer, antiaging effects, they can also eliminate oxidative radicals ($^{-}$OH, O_2 and H_2O_2) and anti-inflammatory in the digestive system, as well as protecting the liver. However, there is little information on the use of papaya flour in agri-food products of technological interest, so it is a source of opportunity for the development of new research.

Conflict of Interest

The authors declare no conflict of interest.

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