TIP Revista Especializada en Ciencias Químico-Biológicas, 27: 1-14, 2024.
https://doi.org/10.22201/fesz.23958723e.2024.662

Lactic acid fermentation in papaya (*Carica papaya* L.): impact on antioxidant compounds, human health, and byproducts valorization

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Abstract

Lactic acid fermentation (LAF) of papaya is a biotechnological strategy that has been understudied, although it holds great potential. Nevertheless, it can be of interest for various opportunities across industries, transforming this fruit into a valuable resource. The aim of this review article is to focus on the impact on antioxidant capacity, health benefits, and the valorization of papaya byproducts through LAF. LAF is a strategy to promote an increase in the concentration of antioxidant compounds, such as phenolic compounds in papaya. Lactic acid bacteria (LAB) release and modify these compounds during fermentation, potentially enhancing their antioxidant capacity. Products generated from the LAF of papaya have shown potential anti-hypercholesterolemic effects, antiviral properties, and the production of protein hydrolysates with antioxidant potential. Papaya leaves, peels, and waste can be revalorized using LAF to extract bioactive compounds of interest for the pharmaceutical, cosmetic, or food industries. Papaya is a good source of fiber and simple sugars, and given the great diversity of LAB, the development of prebiotics and the selection of possible probiotics adapted to plant media are feasible. Although significant progress has been made in understanding its health benefits and byproduct valorization, further research is needed to comprehend its scope and develop specific products fully.

Keywords: lactic acid fermentation, papaya, antioxidant compounds, health, papaya wastes.

Fermentación ácido-láctica en papaya (*Carica papaya* L.): impacto en compuestos antioxidantes, salud humana y valorización de subproductos

Resumen

La fermentación ácido-láctica (FAL) de la papaya es una estrategia biotecnológica que, aunque tiene mucho potencial, ha sido poco estudiada. Sin embargo, puede ser de interés para una serie de oportunidades en diversas industrias, transformando este fruto en un recurso valioso. El objetivo de este artículo de revisión se enfoca en el impacto de la capacidad antioxidante, los beneficios para la salud y la valorización de los subproductos de la papaya a través de la FAL. La FAL es una estrategia para promover el incremento de la concentración de compuestos antioxidantes, como los compuestos fenólicos en la papaya. Las bacterias ácido lácticas (BAL) liberan y modifican estos compuestos durante la fermentación, lo que potencialmente mejora su capacidad antioxidante. Los productos generados de la FAL de la papaya han demostrado posibles efectos antihipercolesterolémicos, propiedades antivirales y la producción de hidrolizados de proteínas con potencial antioxidante. Las hojas, cáscaras y desechos de la papaya se pueden revalorizar, utilizando la FAL como proceso de extracción de compuestos bioactivos de interés para la industria farmacéutica, cosmética o alimentaria. La papaya es una buena fuente de fibra y azúcares simples y dada la gran diversidad de BAL, es factible el desarrollo de prebióticos y selección de posibles probióticos adaptados a medios vegetales. Si bien se han realizado avances significativos en la comprensión de sus beneficios para la salud y la valorización de los subproductos, se necesita más investigación para abarcar completamente su alcance y desarrollar productos específicos.

Palabras clave: fermentación ácido láctica, papaya, compuestos antioxidantes, salud, desechos de papaya.

Artículo recibido el 03 de noviembre del 2023.
Artículo aceptado el 25 de julio del 2024.

INTRODUCTION

Lactic acid fermentation (LAF) is a metabolic process carried out by lactic acid bacteria (LAB) to obtain energy, and its products include lactic acid and other metabolites such as ethanol, acetic acid, and carbon dioxide (Vivek *et al*., 2019; Eiteman & Ramalingam, 2015; Stincone *et al*., 2015). Fermentation has been embraced as a viable, sustainable, low-cost technology to preserve and enhance the nutritional properties of foods (Ruíz Rodríguez, Mendoza, Van Nieuwenhove, Pescuma & Mozzi, 2020). LAF has gained interest as a differentiation strategy for papaya-derived juices and purees and the development of functional foods.

Papaya (*Carica papaya* L.) is a rich source of antioxidants such as carotenoids, phenolic compounds, and other phytochemicals, which play a crucial role in promoting health and perverting diseases (Insanu *et al*., 2022; Leitão, Ribeiro, García, Barreiros & Correia, 2022). These antioxidants can combat oxidative stress in the body, a factor associated with various chronic diseases and premature aging. In this context, fermented foods like papaya puree and juice with high antioxidant potential have been developed (Mashitoa *et al*., 2021; Chen, Chen, Chen, Zhang & Chen, 2018). It has been observed that LAF can further enhance this antioxidant capacity, and these products have shown promise in combating conditions like hypercholesterolemia and preventing viral infections (Setiarto, Widhyastuti, Octavia & Himawan, 2018; Haddad *et al*., 2020).

Inevitably, the cultivation and processing of papaya generate significant volumes of waste, such as the peel, leaves, and pulp residues. These byproducts can be utilized as a carbon source, significantly enhancing the content of phenolic compounds and antioxidant capacity (Ngouénam *et al*., 2021; Yang, Tan & Cai, 2016; So'aib, Hamid, Salihon & Tan, 2020a; So'aib, Hamid, Salihon, Tan & Harmid, 2020b). Research on LAF of papaya and its byproducts is a continuously growing field with the potential to reduce biomass waste and offer innovative products with health benefits. In combination, papaya and its byproducts represent a valuable source of natural antioxidants that positively impact human health and well-being. However, research is limited regarding the LAF of papaya byproducts, such as the peel, seeds, and leaves. New studies are needed to advance the development of differentiated papaya products.

No fruit processing technology is 100% efficient, and waste contains a portion of the edible part, so they are still a reservoir of nutrients and compounds of interest (Pathak, Mandavgane & Kulkarni, 2019). It is estimated that by 2024, approximately 123,096 tons of shell and around 97,562 tons of waste pulp will be produced in Mexico, both with a significant amount of bioactive compounds such as carotenoids and phenolic acids, will be discarded (Leitao *et al*., 2022). LAF can be a form of sustainable papaya waste management, which could contribute to environmental, economic, and food-related improvements. This review article aims to provide the reader with a comprehensive overview of the influence of LAF on the potential enhancement of antioxidant capacity, its health benefits, and the valorization of papaya byproducts. Furthermore, it emphasizes the importance of conducting new research to explore the various functionalities of fermented papaya products.

Research was conducted on various specialized search engines to collect relevant scientific information. The search engines used ScienceDirect, Google Scholar, PubMed, Scopus, and Redalyc. Keywords such as "lactic acid fermentation", "lactic acid bacteria", and "fermentación ácido láctica" were combined with terms like "papaya fruit", "papaya wastes", "papaya peel", and "papaya leaf". The publications obtained were classified into different thematic groups: 1) Antioxidant compounds of papaya derivatives: their underutilization in the food industry and their environmental impact, 2) Lactic acid fermentation and its influence on papaya's antioxidant compounds, 3) Exploring potential health benefits of fermented papaya foods, 4) Papaya byproducts: lactic acid fermentation for valorization, 6) Lactic acid fermentation in papaya: a glimpse into the future of its applications. Priority was given to including studies published in the last five years, although some earlier relevant publications related to the topic were also considered.

Antioxidant compounds of papaya derivatives: Their underutilization in the food industry and their environmental impact

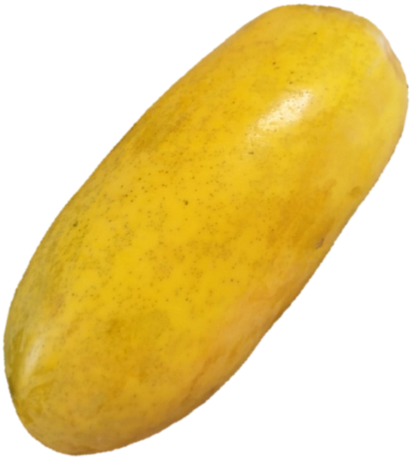
Carica papaya L. is a tropical fruit widely cultivated in warm climate regions worldwide. It is a rich source of vitamins, minerals, and other health-beneficial nutrients (Dotto & Abihudi, 2021). Furthermore, papaya is recognized for its content of antioxidants, which are natural compounds that help protect the body's cells against oxidative damage (Jiao *et al*., 2022). In particular, papaya peel and pulp contain a significant amount of antioxidants, giving them great potential to produce functional foods or nutraceuticals (Dotto & Abihudi, 2021; Jiao *et al*., 2022). This section will explore the quantity and type of antioxidants present in papaya peel and pulp and their wastage in the food industry.

Some studies have identified the main antioxidants present in papaya peel. Among the bioactive compounds identified are alkaloids, phenolic acids, flavonoids, phytosterols, and saponins (Calvache, Cueto, Farroni, de Escalada Pla & Gerschenson, 2016; Insanu *et al*., 2022). Additionally, ascorbic acid, carotenoids, and phenolic compounds have been discovered (Calvache *et al*., 2016). In studies conducted by Calvache *et al*. (2016), five phenolic compounds were found, including protocatechuic acid hexosides, manghaslin, quercetin 3-O rutinoside, caffeic acid hexosides, and ferulic acid. Four carotenoids, including lutein, zeaxanthin, β-carotene, and β-cryptoxanthin, were also detected. Similarly, Insanu *et al*. (2022) described the presence of 31 polyphenols in different papaya varieties, including 16 phenolic acids, 3 lignans, 1 flavanol, 2 dihydrochalcones, and 9 flavonols. However, further research is needed to determine more specific antioxidant compounds in papaya peel.

Like in papaya peel, antioxidants have also been identified in papaya pulp. Papaya pulp contains a variety of phenols, according to Kelebek, Selli, Gubbuk & Gunes (2015), who determined the profiles in the pulp of papaya varieties Sel-42 and Tainung. Among the identified compounds are *p*-hydroxybenzoic acid, protocatechuic acid hexoside, protocatechuic acid, chlorogenic acid, caffeic acid, ferulic acid, kaempferol-3-O-glucoside, and myricetin. The same authors detected in lower concentrations gallic acid deoxhihexoside, caffeoyl hexose-deoxihexoside, rutin, *p*-coumaric acid, and gallic acid hexoside. On the other hand, Gayosso-García Sancho, Yahia & González-Aguilar (2011) identified lycopene, β-carotene, and β-cryptoxanthin in papaya pulp. Meanwhile, Jeon, Chung, Kim & Lee (2022) detected three phenolic acids in pulp-peel Tainung No. 2 papaya extracts: chlorogenic acid, cynarin, and neochlorogenic acid. Two flavonoids were also detected (eupatorin and vicenin II). Knowing the specific compounds in these residues is important because it can help understand their potential benefits.

Due to the wide variety and complexity of individually identifying each phenolic or carotenoid compound, most studies report the total content of each type of compound. Maradol papaya peel contains higher amounts of total phenols and flavonoids (600 mg Galic Acid Equivalents (GAE)/100 g and 1,000 mg Quercetin Equivalents (QE)/100 g, respectively) than the pulp, which has lower values (around 400 mg GAE and 700 mg QE/100 g) (Ovando-Martínez *et al.*, 2018). In the peel, the main compounds (Figure 1 and 2) are *p*-coumaric acid (135.64 to 229.59 mg/100 g), ferulic acid (166.63 to 277.49 mg/100 g), and caffeic acid (112.89 to 175.51 mg/100 g) (Ovando-Martínez & González-Aguilar, 2020; Saeed *et al*., 2014). While in the pulp, they are found in smaller quantities (Ovando-Martínez & González-Aguilar, 2020). Additionally, the peel has a higher concentration of carotenoids (2,500 mg/100 g Fresh Weight (FW)) than the pulp (800 mg/100 g FW) due to the presence of cryptoxanthin, α-carotene (425 μg/100 g FW), β-carotene (800 μg/100 g FW), lycopene (<400 μg/100 g FW), lutein (1,600 μg/100 g FW), and zeaxanthin (400 μg/100 g FW) (Ovando-Martínez *et al*., 2018). Due to their antioxidant properties, these compounds can be used as food ingredients.

The consumption of fresh papaya inevitably leads to the generation of waste, primarily peel and small amounts of pulp, limiting the possibility of harnessing its antioxidant properties. On average, it is estimated that 11% of the pulp goes unused, while in the peel case, only 8% of the total peel is recovered (Ovando-Martínez *et al*., 2018). Although these values may vary depending on various factors such as fruit variety and ripeness, it has been reported that papaya peel can represent approximately 12% of the total fruit weight (Romo-Zamarrón, Pérez-Cabrera & Tecante, 2019). Despite the lack of recent data on the amount of peel lost in the papaya production chain in Mexico, it is expected that by the year 2030, around 136,675 tons of peel and 108,325 tons of pulp will be wasted. The estimates are based on production values published by Secretaría de Agricultura, Ganadería, Desarrollo Rural, Pesca y Alimentación (SAGARPA , 2017), the percentages that the peel represents of the total fruit (Sharma, Joshi, Sharma, Bachheti & Husen, 2020), and the amount of pulp and peel that goes unused (Ovando-Martínez *et al*., 2018). According to this prediction, there is a considerable amount of papaya peel and pulp waste.



β-carotene (800 μg/100 g DW)

α-carotene (425 μg/100 g DW)

Lycopene (<400 μg/100 g DW)

Lutein (1600 μg/100 g DW)

Zeaxanthin (400 μg/100 g DW)

***p*-cumaric acid (135.64 a 229.59 mg/100g)**

Cafeic acid (112.89 a 175.51 mg/100 g)

Ferulic acid (166.63 a 277.49 mg/100 g)

Note: these values may vary depending on the variety and degree of maturity of the papaya

Figure 1. Main antioxidant compounds present in papaya peel (Adapted from Ovando-Martínez & González-Aguilar, 2020).

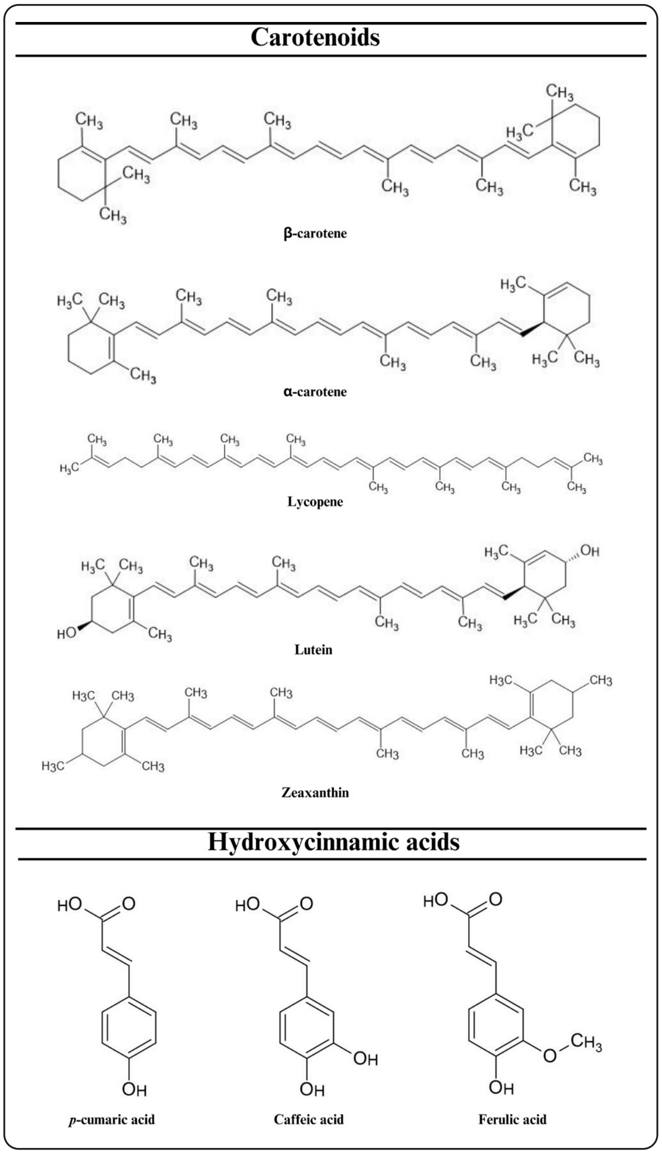


Figure 2. Chemical structure of key antioxidant compounds found in papaya peel. The figure was made from personal creativity.

It is important to highlight that papaya production in Mexico is constantly growing. According to SAGARPA data (2017), there is an expected 12.30% increase from the years 2016 to 2024, with an additional 17.76% increase by the year 2030. While the discarded peel and pulp are biodegradable, they have become an environmental issue due to the large volumes generated. There is limited information about the actual quantity of discarded peel and pulp, as records do not cover most small and medium-scale producers, but it is believed to represent a significant portion of the total production (Ovando-Martínez & González-Aguilar, 2020). Therefore, more specific studies are needed to determine the actual amount of waste and establish strategies for utilizing papaya remains.

In Mexico, there is no industry dedicated to generating papaya-derived products, which could be because there is sufficient production to meet national demand and even become the world's leading exporter of papaya (SAGARPA, 2017). While there is no precise data on losses due to papaya waste and its residues, this will depend on local waste disposal regulations, according to Secretaría de Medio Ambiente y Recursos Naturales (SEMARNAT, 2020). The main papaya producers in Mexico are Oaxaca (32.7%), Colima (16.5%), Chiapas (13.6%), and Veracruz (10.9%) (SAGARPA, 2017). However, these states are also the poorest in Mexico, according to Consejo Nacional de Evaluación de la Política de Desarrollo Social (CONEVAL, 2022), with over 51% of the population in these states living in poverty. Despite Mexico being the leading producer and exporter of papaya, this doesn't address the social issue of poverty. Therefore, transforming papaya fruit and utilizing its peel and pulp residues to create functional foods could result in fewer losses and more profits, adding value and improving the economic situation in these regions.

The United Nations Environment Programme (UNEP) estimates that 8% and 10% of global greenhouse gas emissions are related to unconsumed food (UNEP, 2021). However, there is no specific data on greenhouse gas emissions associated with papaya waste in Mexico. The organic remnants of the fruit, such as peel and pulp, can produce methane (CH_4) and carbon dioxide (CO_2) when they decompose in landfills or during composting processes without proper control (Dávila & Sierra, 2018). Furthermore, accumulating these residues can contaminate the soil and release greenhouse gases and chemicals that affect soil and nearby groundwater quality (Barret, 2017; Dávila & Sierra, 2018). The decomposition of organic matter can also generate unpleasant odors and attract insects and rodents, which can harm human health and the environment (Dávila & Sierra, 2018). Therefore, precise figures are needed to understand the environmental impact of papaya waste better.

The information about papaya waste and the consequent loss of its phenolic compounds and carotenoids is crucial today. The fact that these compounds are lost during processing implies an economic loss for the food industry and a negative impact on the environment. Consequently, this information underscores the importance of developing strategies to reduce papaya waste and preserve its compounds, which can help improve food security.

Lactic acid fermentation and its influence on antioxidant compounds in papaya

Bacteria belonging to the *Lactobacillus* genus have been used in the LAF of plant substrates with promising results. This is because these bacteria originated in plants but developed the ability to survive in the intestines of animals whose diet was primarily plant-based (Duar *et al*., 2017). As a result, the LAF of fruit waste has become an option to obtain metabolites of interest or use them as food ingredients. These bioproducts are rich in vitamins, minerals, dietary fiber, and antioxidant compounds (Yang *et al*., 2016).

Several premises explain why fermentation with LAB can increase the concentration of phenolic compounds. First, it has been observed that some LAB strains could metabolize carbohydrates from the plant cell wall, such as xylose, arabinose, rhamnose, and fucose (Pot *et al*., 2014). This process leads to the release of phenolic compounds that are bound to cell wall constituent sugars, thereby increasing their bioactivity and bioaccessibility (Wang, Zhang & Lei, 2021; Ricci *et al*., 2018; Kaprasob, Kerdchoechuen, Laohakunjit, Sarkar & Shetty, 2017). Another premise is that LAB possesses enzymatic mechanisms to convert high molecular weight compounds into simpler compounds with higher bioactivity (Carrasco, Lucena-Padros, Brenes & Ruiz-Barba, 2018; López *et al*., 2017). For example, it has been shown that certain strains of *Lactiplantibacillus plantarum* (*Lpb. plantarum*) can degrade tannins by expressing the enzyme tannase (EC: 3.1.1.20) in media containing tannic acid. This enzyme catalyzes the hydrolysis of ester bonds in hydrolyzable tannins and gallic acid esters, which are potent antioxidants (Singh, Kundu, Das & Banerjee, 2019; Hur, Lee, Kim, Choi & Kim, 2014).

The pH is another factor that influences the structural changes that phytochemicals undergo during the process of LAF. A notable example is the behavior of anthocyanins, which are pigments responsible for the color of foods and can undergo isomerization depending on the pH. Anthocyanins are stable in a low pH range (1-2). Therefore, a lower pH can increase the antioxidant capacity of the final product (Hur *et al*., 2014; Borkowski, Szymusiak, Gliszczyńska-Świgło, Rietjens & Tyrakowska, 2005).

In summary, it is difficult to precisely trace the path followed by LAF to increase the phenolic content in fermented plant substrates. However, research indicates that LAF may influence the concentration of phenolic compounds in papaya. In this context, the impact of LAF on the main phenolic compounds present in papaya pulp will be examined. This is because significant information has not been found in the literature regarding fermentation to increase the phenolic content in papaya peel.

Additionally, in the study conducted by Di Cagno, Minervini, Rizzello, De Angelis & Gobbetti (2011), the effect of LAF on the content of polyphenols and the antioxidant capacity of a green smoothie containing papaya as one of its ingredients was evaluated. This smoothie was composed of 40% w/w kiwi, 7% w/w fennel, 8% w/w spinach, and 15% w/w papaya. A mixture of strains of *Lpb. plantarum* K3 and F6, *Lpb. pentosus* P1, and *Weissella cibaria* (*W. cibaria*) B1 and P9 were used to ferment. However, the results showed that fermentation did not increase the total polyphenol content or the antioxidant capacity of the smoothie. Despite this, it was observed that fermentation helped maintain the stability of these compounds during storage, which extended to 30 days at temperature of 4 °C.

Chen *et al*. (2018) reported that the fermentation of papaya juice with *Lpb. plantarum* GIM1.140 and *Lactobacillus acidophilus* (*L. acidophilus*) GIM1.731 produced different results in terms of antioxidant capacity. After 48 h of fermentation with *Lpb. plantarum* GIM1.140, a higher antioxidant capacity was demonstrated, while *L. acidophilus* GIM1.731 reduced the antioxidant capacity of the juice. As for the total phenolic content in the juice fermented with *L. acidophilus* GIM1.731 decreased by approximately 15% after 48 h, while with *Lpb. plantarum* GIM1.140, the decrease was 8%. In the same study, the antioxidant capacity values varied depending on the method used. After 48 h of fermentation, *L. acidophilus* GIM1.731 showed a 32.7%, 6.96%, 20.5%, and 6.5% decrease by the DPPH, ABTS, FRAP, and CUPRAC methods, respectively. In the case of *L. acidophilus* GIM1.731, there was a slight increase of 4.5% (DPPH), 3.6% (FRAP), and 24.6% (CUPRAC), while the ABTS method did not show any growth.

In another study by Mashitoa *et al*. (2021), it was observed that the fermentation of pasteurized papaya puree with strains of *Lpb. plantarum* 75, *Leuconostoc pseudomesenteroides* (*Leu. pseudomesenteroides*) 56, and *W. cibaria* 64 increased the antioxidant capacity, especially the strains *Lpb. plantarum* 75 and *W. cibaria* 64, which showed a significant increase from 1.4 µmol TE/100g to 2.8 and 2.7 µmol TE/100g, respectively. There was also an increase in total phenols (mg GAE/100 g FW) from 303.9 to 475.1 and 467.1 for *Lpb. plantarum* 75 and *W. cibaria* 64, respectively. In conclusion, the results of the study by Mashitoa *et al*. (2021) show that the fermentation of papaya puree with specific LAB strains can significantly increase the antioxidant capacity and total phenols.

More specifically, Mashitoa *et al*. (2021) found that fermentation with strains of *Leuc. pseudomesenteroides* 56, *W. cibaria* 64, and *Lpb. plantarum* 75 increased catechin levels from 14.21 to 66.1, 58.2, and 51.7 mg/kg, respectively. For epicatechin, an increase was observed from 6.2 to 16.9 mg/kg in the case of *Leuc. pseudomesenteroides* 56, to 58.2 mg/kg for *W. cibaria* 64, and 51.7 mg/kg for *Lpb. plantarum* 75. Additionally, an increase in *p*-coumaric acid from 23.7 to 37.4 mg/kg was detected with *Leuc. pseudomesenteroides* 56. Regarding ferulic acid, both *Leuc. pseudomesenteroides* 56 and *Lpb. plantarum* 75 increased from 12.6 to 20.5 and 14.3 mg/kg, respectively. These results suggest that LAF can significantly influence the antioxidant capacity of papaya juice.

LAF technology has even been investigated in the spontaneous fermentation of papaya leaves to evaluate their antioxidant capacity and phenolic compound content (So'aib *et al*., 2020a).

In this study, the formulation consisted of 10% w/v papaya leaves, 10% w/v unrefined sugar, and the remaining distilled water. The results revealed a significant increase in the total polyphenol content, from 5.71 to 31.14 mg GAE/g, and an increase in the antioxidant capacity from 130.5 to 405.8 mM TE. The same study agrees that these results are due to the release of phenolic compounds resulting from the breakdown of glucosidic bonds and esters of phenolic polymers, leading to the formation of simpler structured phenolic compounds. This research suggests that LAF can be an effective strategy for enhancing the content of phenolic compounds and the antioxidant capacity of formulations containing papaya leaves, which has significant implications for their application in the valorization of byproducts as mechanisms for extracting bioactive compounds present in plant waste and the development of functional foods.

In general, the previous studies highlight the influence of LAF and the importance of selecting the right microbial strains to obtain papaya products with enhanced antioxidant properties. They also emphasize the need for further research, especially concerning the fermentation of papaya peel, to harness its content of bioactive compounds and maximize the nutritional value of papaya byproducts.

Exploring the potential health benefits of fermented papaya foods

Fermented papaya-derived products provide an option for preserving or flavoring food and offer a range of significant health benefits. Papaya, with its abundance of bioactive compounds such as antioxidants, enzymes, and other phytochemicals, has gained attention as a focal point in the search for functional foods that promote well-being (Ugbogu *et al*., 2023; Leitão *et al*., 2022). In this context, papaya fermentation emerges as a promising strategy to enhance its beneficial properties, offering a variety of bioactive compounds that can have a positive impact on health (Mashitoa *et al*., 2021; Haddad *et al*., 2020; Chen *et al*., 2018). This section explores the potential positive health effects of fermented papaya products, focusing on the involved bioactive compounds and their potential applications in promoting human well-being.

As mentioned, one of the prominent effects attributed to papaya LAF is related to the potential increase in phenolic compounds with antioxidant properties (Mashitoa *et al*., 202; Chen *et al*., 2018). This possible increase is associated with the release of these compounds from the fruit's cell wall sugars, collectively constituting dietary fiber (DF) (Wang *et al*., 2021; Ricci *et al*., 2018; Kaprasob *et al*., 2017). Although certain studies have evaluated changes in the total phenol content and antioxidant capacity of these fermented foods, the bioaccessibility of these compounds has been addressed in only a few investigations (Mashitoa *et al*., 2021). Bioaccessibility is a critical factor in anticipating the availability of these compounds for absorption, as phenolic compounds interact with DF, which can reduce their bioaccessibility (Rocchetti *et al*., 2022). These interactions occur through hydrogen bonds, electrostatic forces, and ester bonds due to the hydrophobic aromatic rings and hydrophilic groups in the phenolic compounds (Dobson *et al*., 2019; Rocchetti *et al*., 2022).

DF cannot be fully digested in the human digestive system due to the lack of appropriate enzymes for its degradation, which releases some non-extractable phenolic compounds during fermentation in the large intestine (Figure 3). In this context, they can exert their antioxidant action in this part of the digestive system (Palafox-Carlos, Ayala-Zavala & González-Aguilar, 2011; Quirós-Sauceda *et al*., 2014). Although this process contributes to protecting the large intestine from oxidative stress, it would be interesting to explore the possibility of promoting the accessibility of these phenolic compounds and improving their bioactivity, bioaccessibility, and bioavailability through papaya LAF intended for human consumption (Figure 4). Therefore, further research is recommended to delve deeper into this perspective.

Similarly, LAB involved in LAF and present in the consumed food also encounter challenges during gastrointestinal digestion. LAB face multiple hurdles that can affect their viability and activity (Pupa *et al*., 2021). The acidic environment of the stomach can be particularly detrimental to LAB, as many may be destroyed by gastric acid before reaching the intestine. Additionally, digestive enzymes present in the stomach and small intestine can degrade LAB cells, reducing their number and activity (İnce Palamutoğlu, Köse & Baş, 2023). LAB also must compete with other bacteria in the gastrointestinal tract, some of which may be pathogenic and produce substances that inhibit their growth. Moreover, not all LAB can adhere to or be absorbed at the intestinal level, which can result in their excretion in feces (Alp & Kuleaşan, 2020). Despite these challenges, some LAB strains can modulate the hosts immune response by interacting with immune cells in the intestine. Although digestion can affect LAB viability, some strains can survive and exert their beneficial effects in the gastrointestinal tract.

The anti-hypercholesterolemic potential of papaya juice fermented by LAB has been investigated. In a study by Setiarto *et al*. (2018), papaya juice was fermented using three mixed cultures: one composed of *Lactobacillus bulgaricus*, *L. acidophilus*, and *Streptococcus thermophilus*, another with *Lpb. plantarum*, *L. acidophilus*, *S. thermophilu*s, and a third using *Lacticaseibacillus casei*, *L. acidophilus*, and *S. thermophilus*. Subsequently, tests were performed in a murine model with Sprague Dawley strain rats in which hypercholesterolemia was induced. The study results revealed that papaya juice fermented with a mixed culture of *L. bulgaricus*, *L. acidophilus*, and *S. thermophilus* reduced cholesterol levels by 17.51%, while

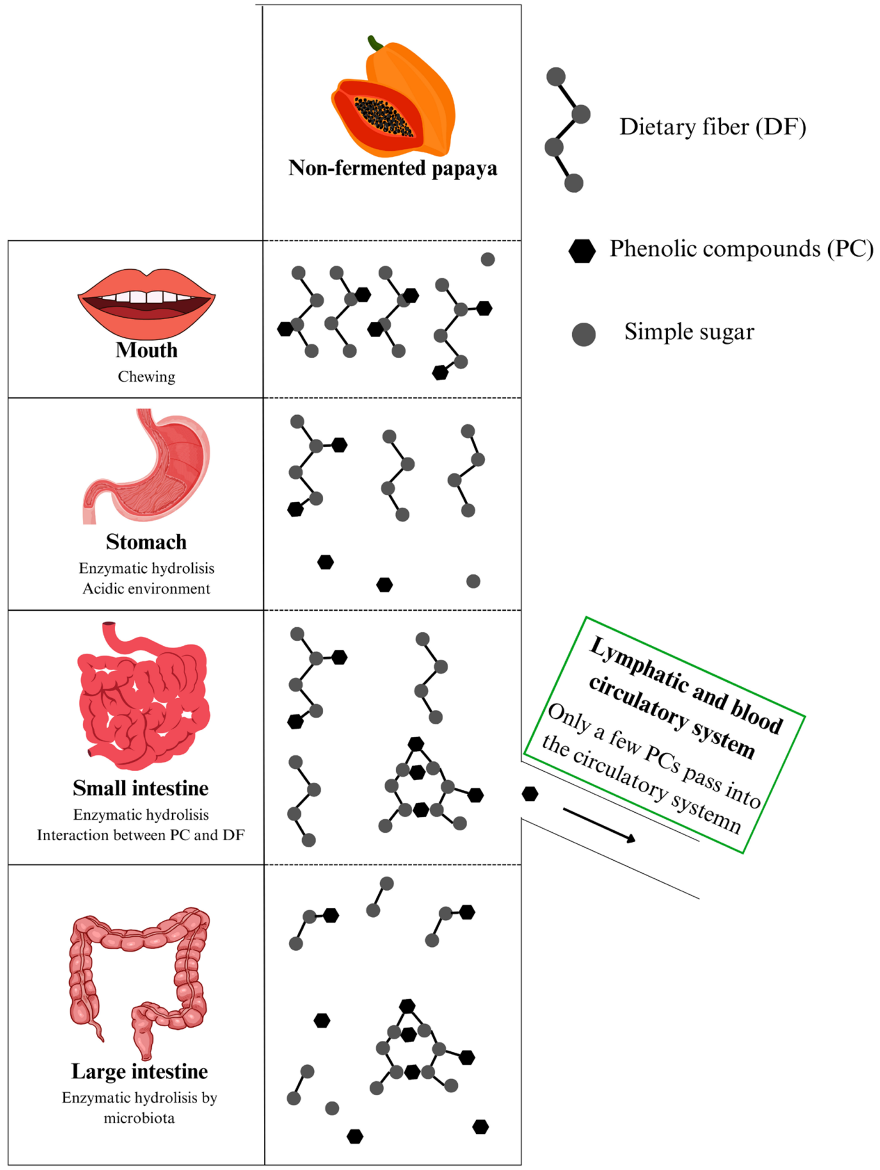


Figure 3. Potential bioabsorption of phenolic compounds in non-fermented papaya fruit (Adapted from Palafox-Carlos *et al*., 2011).

the positive control group treated with the drug simvastatin showed a reduction of 22.56%. The authors suggest that this formulation could apply to humans at a concentration of 55.56 mL per day, although additional clinical studies are needed to verify its effectiveness.

An interesting property has been assessed following the LAF of papaya puree. In a study conducted by Haddad *et al*. (2020) papaya puree was fermented using strains of *Lpb. plantarum* 75, *W. cibaria* 64, and *Leuc. pseudomesenteroides* 56. The results of this study demonstrated a reduction in the number of human cells infected with the Zika virus, which was dependent on the strain used in the fermentation. Specifically, it was observed that fermentation with *Lpb. plantarum* 75 and *Leuc. pseudomesenteroides* 56 decreased the antiviral activity of papaya pulp by 5 to 6 times compared to non-fermented pulp. On the other hand, fermentation with *W. cibaria* 64 reduced this activity by nearly 14 times. This means that a concentration of 1.5, 1.8, and 4.2 mg/mL of fermented papaya extract with *Lpb. plantarum* 75, *Leuc. pseudomesenteroides* 56 and *W. cibaria* 64, respectively, was required to inhibit 50% of the viral activity of the Zika virus. Although a higher extract concentration was needed to achieve inhibition in the case of *W. cibaria* 64, this study demonstrated that papaya puree could inhibit the infection

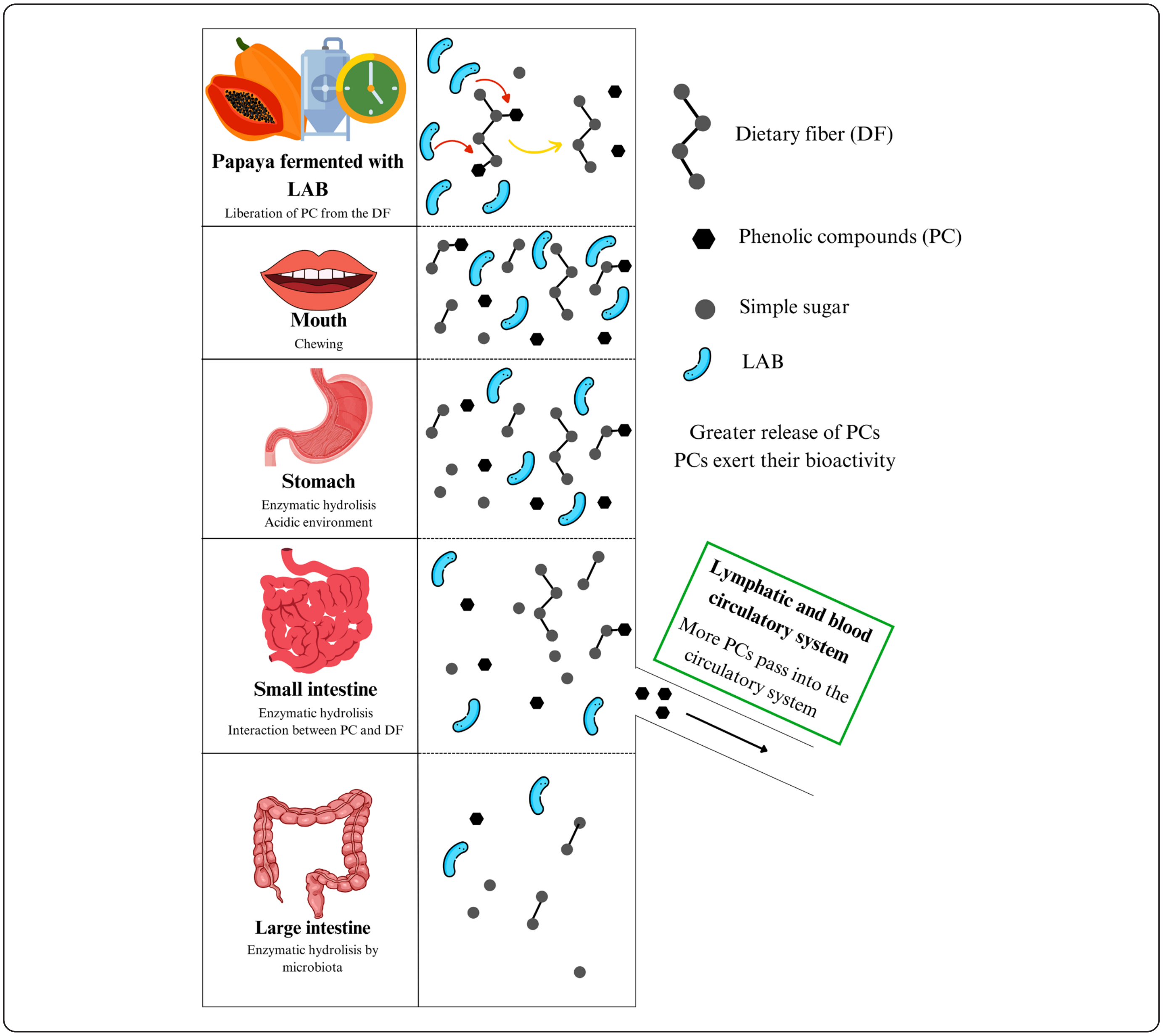


Figure 4. Potential bioabsorption of phenolic compounds in papaya fruit fermented with LAB. The figure was made from personal creativity.

of human cells by the Zika virus. This antiviral property could have significant applications in preventing and treating viral diseases, although further research is required to understand its scope and mechanisms of action fully.

LAF has also been considered for producing protein hydrolysates with potential antioxidant properties. In a study conducted by Carballo-Sánchez *et al*. (2016), papaya was fermented using strains of *Lpb. plantarum* and a mixture of tuna byproducts, including heads, bones, viscera, and black meat. During this process, the highest degree of hydrolysis reached an impressive 87.81% after 120 hours of fermentation. Furthermore, this study also evaluated the minimum concentration of protein hydrolysate needed to achieve 50% of antioxidant activity. It was found that this lower concentration was obtained at 72 hours of fermentation and was 5.75 µg/g of protein. These results highlight that papaya can serve as a valuable source of carbon that can be combined with other protein-rich byproducts like tuna to obtain protein hydrolysates with high nutritional value and potential health benefits. This work demonstrates how LAF can be effectively used to enhance the availability of proteins and antioxidants in papaya-based products, which could have significant benefits in terms of both nutritional value and health (Nirmal, Santivarangkna, Benjakul & Maqsood, 2022; Carballo-Sánchez *et al*., 2016). However, it is important to note that while LAF can produce protein hydrolysates, the papaya protease enzyme (papain), can also break down proteins to form bioactive protein hydrolysates (Noman *et al*., 2018).

The research supports the idea that LAF of papaya can be a promising strategy for obtaining foods that promote human health (Table I). However, it is also evident that there is still much to be done in this research area. More clinical studies and experiments are needed to fully understand the extent of the benefits and develop specific products that maximize the potential of LAF in terms of health and well-being. Additionally, it is important to consider food safety aspects and process standardization before these products can be widely used and commercialized. In summary, LAF of papaya is an area of research with much to discover and develop.

Papaya byproducts: Lactic acid fermentation for valorization

Papaya, known for its rich pulp and exquisite flavor, also generates byproducts such as the peel, seeds, and leaves, which are often discarded or underutilized (Vázquez-Mata, Acosta-Camacho, Camacho-Parra, Rocha-Mendoza & Cano, 2022; Pathak *et al*., 2019). However, LAF emerges as a promising technique to maximize the potential of these byproducts, transforming them into valuable resources loaded with bioactive compounds.

Using papaya residues as an alternative carbon source to promote LAB growth and lactic acid production has been proposed (Ngouénam *et al*., 2021; Yang *et al*., 2016). Lactic acid is essential in various industries due to its versatility and wide applications. In the food industry, it serves as an acidulant and preservative, playing a crucial role in dairy product fermentation and the production of probiotic foods (Ameen & Caruso, 2017). In the pharmaceutical field, lactic acid is used in drug formulations and dermatological products (Daba & Elkhateeb, 2020; Ameen & Caruso, 2017). Furthermore, this compound is a fundamental component in the cosmetics industry, where its exfoliating and moisturizing properties are harnessed in skincare products. In the chemical industry, lactic acid is a raw material for producing biodegradable polymers and other compounds (Ameen & Caruso, 2017). It also finds applications related to the textile industry and the production of biodegradable packaging (Perin *et al*., 2020).

Similarly, the native fermentation of papaya leaves has been explored to promote the extraction and increase the total phenol content, enhancing its antioxidant activity (So'aib *et al*., 2020a, 2020b). In summary, utilizing papaya byproducts through LAF is a promising yet underexplored strategy.

Lactic acid fermentation in papaya: A glimpse into the future of its applications

As research and innovation continue to advance in papaya fermentation, exciting prospects for its application in various sectors are revealed, from the food industry to pharmaceuticals and cosmetics. Papaya is a highly valued fruit in the food industry due to its versatility and the variety of products that can be derived from it. Additionally, it undergoes processing to extend its shelf life (Sharma *et al.*, 2020). Papaya can be used to produce beverages, juices, nectars (Bahnas *et al*., 2019; Sharma *et al*., 2020), jams, jellies (Hunaldo *et al.,* 2020), sweets (Pathak, Dubey & Verma, 2021), and ice creams (Hong, Rajan & Pui, 2021). As a future perspective, probiotic non-dairy products could be developed by adding potential probiotic LAB to all of these products. Papaya also produces enzymes for the food industry, alcoholic beverages, animal feed, and dietary supplements (Chavan, 2018; Cholassery *et al*., 2019; Sharma *et al*., 2020). Papaya peel is also a valuable source of dietary fiber and is used in preparing extracts for cosmetic and pharmaceutical use (Sharma *et al*., 2020). In summary, papaya has multiple applications in the food industry.

LAF of papaya waste could further enhance the bioactive compound's potentiation and utility as a functional ingredient. For instance, papaya peel and seeds have been the subject of studies for creating functional foods such as cookies and bread, using different parts of the fruit, including the peel, pulp, and seeds (Bhosale & Udachan, 2018; Joymak, Ngamukote, Chantarasinlapin & Adisakwattana, 2021); Pavithra, Devi, Suneetha & Rani, 2018). However, the effect of LAF on these ingredients has not been evaluated yet. Moreover, the fermentation of papaya leaves to harness their antioxidant potential has already begun (So'aib *et al*., 2020a, 2020b).

However, when it comes to applying LAF in the context of papaya, we are in a recent field of opportunity that is gaining momentum. Regarding food production, research has developed fermented beverages and juices with LAB to increase phenolic compounds and enhance antioxidant capacity (Mashitoa *et al*., 2021; Chen *et al*., 2018). Fermentation of papaya juices combined with milk for similar purposes has also been explored, as well as the fermentation of papaya puree to create fermented foods (Chen *et al*., 2018; Setiarto *et al*., 2018). These functional foods could play a prominent role in the future food industry.

LAF in papaya opens the door to various functionalities beyond antioxidant properties. For instance, research can be conducted into anti-hypercholesterolemic properties (Setiarto *et al*., 2018), the antiviral potential (Haddad *et al*., 2020), and the production of protein hydrolysates from papaya LAF (Carballo-Sánchez *et al*., 2016). These advances in applying LAF in papaya promise to transform how we view and harness this fruit across various diverse sectors.

Table I. Impact on the bioactivity and concentration of bioactive compounds present in papaya products fermented with lactic acid bacteria.

Product	Bacteria	Strain	Type of study	Bioactivity / Bioactive compound	References
Pasteurized papaya puree	*Lactiplantibacillus plantarum*	75	*In vitro*	↑ Total phenols ↑ Antioxidant capacity (FRAP) ↑ Recovery of phenolic compounds in gastrointestinal simulation ↑ % inhibition of α-glucosidase	Mashitoa *et al*., 2021
	Weisella cibaria	64		↑ Total phenols ↑ Antioxidant capacity ↑ Recovery of phenolic compounds in gastrointestinal simulation	
	Leuconostoc pseudomesenteroides	56		↑ Total phenols ↑ % inhibition of α-glucosidase	
Papaya juice	*Lactobacillus acidophilus*	GIM1.731		↓ Total phenols ↑ Flavonoids ↓ Carotenoids ↓ Vitamin C ↑ Antioxidant capacity (DPPH y CUPRAC)	Chen *et al*., 2018
	Lactiplantibacillus plantarum	GIM1.140		↓ Total phenols ↑ Flavonoids ↓ Carotenoids ↓ Vitamin C ↓ Antioxidant capacity	
Green smoothie with kiwi, fig, spinach, and papaya	*Lactiplantibacillus plantarum*	K3		↓ Total phenols ↓ Antioxidant capacity Increased stability of ascorbic acid during storage	Di Cagno *et al*., 2011
	Lactiplantibacillus plantarum	F6			
	Lactiplantibacillus pentosus	P1			
	Weisella cibaria	B1			
	Weisella cibaria	P9			
Papaya juice with milk	*Lactobacillus bulgaricus*	*nd*	*In vivo*	↓ 17.51% blood cholesterol	Setiarto *et al*., 2018
	Lactobacillus acidophilus				
	Streptococcus thermophilus				
Papaya puree	*Lactiplantibacillus plantarum*	75	*In vitro*	↓ 5-fold antiviral activity against Zika virus	Haddad *et al*., 2020
	Leuconostoc pseudomesenteroides	56			
	Weisella cibaria	64		↓ 14-fold antiviral activity against Zika virus	
Papaya and *Thunus albacares* protein hydrolysates.	*Lactiplantibacillus plantarum*	APG-Eurozym		87.71% degree of hydrolysis at 120 h of fermentation 5.75 µg/g of protein hydrolysate produced IC$_{50}$ of antioxidant activity.	Carballo-Sánchez *et al*., 2016

nd No data

Conclusions

Lactic acid fermentation can modulate the content of antioxidants, such as phenolic compounds, bioactive peptides, carotenoids, and ascorbic acid, found in papaya and its byproducts. This technique allows for the utilization of a broad range of phytochemicals from papaya, reducing waste and facilitating the development of functional foods, nutraceuticals, as well as potential applications in pharmaceuticals and cosmetics.

These bioactive compounds offer health benefits, including antioxidant capacity, anti-hypercholesterolemic properties and antiviral activity. Despite the promising potential of papaya fermentation, further research is crucial to fully understand its full scope and to develop specific products that harness its transformative potential in various industries.

Acknowledgments

The corresponding author Manuel Vargas-Ortiz, thanks project number 372 “Frutos tropicales como fuente de fenoles y fibra, interacciones moleculares en digestión simulada” of the Investigadores por México program, supported by CONAHCYT.

The authors Jesús Ayala-Zavala and Teresita de Jesús Castillo-Romero acknowledge the financial support provided by CONAHCYT.

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