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A review on biological activities of papaya (*Carica papaya* L.) leaves extract and its potency as an active substance in the food packaging

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Abstract

Active packaging is extensively developed as a promising concept to protect food products while maintaining its quality. Plant extract from papaya leaves has long been known to have antimicrobial and antioxidant activities due to the presence of phenolics and other compounds such as alkaloids, flavonoids, saponin and tannin. Extraction method, solvent type, sample preparation, extraction time and extraction temperature play important roles in extracting these bioactive compounds. The presence of bioactive compounds in papaya leaves extract gives it potentials to be developed into active packaging systems such as biodegradable active packaging or even edible active coatings. In the present review, the roles of bioactive compounds of papaya leaves as an antimicrobial and antioxidant agent are elucidated including their extraction process. In addition, the applications and opportunities of papaya leaves extract as an active substance in the food packaging field are also described.

Introduction

In the last few years, active packaging is one of the innovative developments in the food packaging sector, and poses a challenge for researchers in the related field. The main purpose of this packaging model is to extend the shelf life of packed products by maintaining or even increasing their quality (Dobrucka and Cierpiszewski, 2014). This packaging model can also provide such function due to the incorporation of certain materials as an active substance for the packaging. The role of the active substance is to enhance the performance of packaging system such as absorbing or releasing certain components (Hosseinnejad, 2014) so that the quality of packed products can be maintained.

The incorporation of active substances into the packaging materials is also considered more effective than direct incorporation into the food which could alter the sensorial attributes of the food. In addition, active substances with antimicrobial ability may rapidly be inactivated due to its interaction with food substances or dilution below active concentration (Nguyen Van Long *et al.*, 2016). By using the active packaging concept, active substances in the packaging materials can gradually be migrated or released into the wrapped food products.

However, critical concern related to the selection of active substances has emerged, and that the substances must be safe for consumption. As regulated by the European Regulation 1935/2004/EC (European Standard, 2004), which broadens the possibility for the use of materials and packaging solutions that interact actively with the food and with the head space, all chemicals present in the active system itself, or produced during the food-environment interaction must be defined, controlled, and admitted to the accepted lists, or authorised by the community and labelled, in order to guarantee the safety of the consumers.

Papaya (*Carica papaya* L.) leaves are usually used as herbal therapeutics in certain regions, especially Asia and Africa. The efficacy of papaya leaves has been studied in reducing cardiovascular disease

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risk (Adenowo *et al.*, 2014), relieving allergic, as immune-adjuvant for vaccine therapy, anti-tumour drug (Otsuki *et al.*, 2010), and anti-inflammatory drug (Owoyele *et al.*, 2008). Other studies have also been carried out to test the antimicrobial activity of papaya leaves extract against fungi, yeasts, and Gram-positive and Gram-negative bacteria (Chávez-Quintal *et al.*, 2011; Rahman *et al.*, 2011; Peter *et al.*, 2014). The potency of antioxidant activity of papaya leaves extract has also been documented (Ayoola *et al.*, 2008; Maisarah *et al.*, 2013). These activities are allegedly due to the mode of action of bioactive compounds that are found in the papaya leaves (Yusha'u *et al.*, 2009; Imaga *et al.*, 2010; Vuong *et al.*, 2013; Juárez-Rojop *et al.*, 2014). Thus, the incorporation of papaya leaves extract as an active substance in the packaging materials is essential. Therefore, the objective of this review is to review the antimicrobial and antioxidant activities of papaya leaves extract, as well as its potency and opportunity to be developed in the food packaging sector as an active substance.

Bioactive compounds in papaya leaves and their extraction

Phytochemical compounds found in papaya leaves include alkaloids, saponin, tannin, flavonoids, anthraquinone (free and bound), phlobatannin, cardiac glycosides, terpenoids and proanthocyanidin (Yusha'u *et al.*, 2009; Imaga *et al.*, 2010; Vuong *et al.*, 2013; Juárez-Rojop *et al.*, 2014; Kayalvizhi *et al.*, 2015; Nugroho *et al.*, 2017). These compounds can be obtained through extraction. Soxhlet and maceration are well-known as conventional extraction methods. Both methods are simple, but Soxhlet extraction or hot continuous extraction may cause potential toxic emissions during extraction and thermal decomposition of targeted compounds, while maceration requires a large quantity of solvent as compared to Soxhlet extraction. Therefore, many things must be considered in selecting any extraction methods such as the type of solvent, solvent-sample ratio, extraction time and temperature (Gupta *et al.*, 2012; Azwanida, 2015). In particular, the solvents used should be part of extraction planning, especially the variability of dielectric constants, because it determines the extracted compounds.

Bioactive compounds can be extracted by using various solvents based on the dielectric constant which refers to the polarity; polar, semi-polar or non-polar. Table 1 summarises the most effective solvent in extracting specific bioactive compounds of papaya leaves based on the quantitative analysis. Using different solvents, different compounds will be extracted. Table 1 suggests that ethanol is the most effective solvent. This is possibly due to the possible complex formation of some phenolic compounds that are soluble in ethanol. By referring to the general principle in solvent extraction "like dissolves like", it can be fathomed that papaya leaves extract contains diverse phenolic compounds which have similar polarity with that solvent. Despite ethanol being the most effective solvent, the extraction yield obtained with water is higher than organic solvents (Asghar *et al.*, 2016). Even if using mixtures of organic solvents and water, the water concentration added should be increased. The mixture may facilitate the extraction of all compounds, either water-soluble and/or that are soluble in organic solvents; this contributes to greater extraction yield (Do *et al.*, 2014).

Table 1. Effectivity of solvent type in extracting bioactive compounds of papaya leaves (based on the quantitative analysis).

Bioactive compound	Most effective solvent	Reference
Phenolic compounds (in general)	ethanol	Asghar *et al.* (2016); Vuong *et al.* (2015); Ifesan *et al.* (2013)
	water	Mandal *et al.* (2015)
	acidic water	Nguyen *et al.* (2015)
Flavonoid	ethanol	Asghar *et al.* (2016); Vuong *et al.* (2013)
	acidic ethanol	Nguyen *et al.* (2015)
	water	Mandal *et al.* (2015)
Saponin	ethanol	Vuong *et al.* (2013; 2015)
Tannin	ethanol	Juárez-Rojop *et al.* (2014)
Alkaloid	ethanol	Juárez-Rojop *et al.* (2014)
Proanthocyanidins	ethanol	Vuong *et al.* (2013)

Although water is the safest solvent and reliable, but its effectiveness is lower than ethanol. Asghar *et al.* (2016) demonstrated that water solvent could extract phenolic compounds from papaya leaves, but the effectiveness was still lower than organic solvents (ethanol and methanol). In a study conducted by Do *et al.* (2014) a similar trend was observed but in a different sample.

The type of solvent does not only influence the extracted compounds, but also the antioxidant activity of the extracted compounds. A research conducted by Vuong *et al.* (2013) demonstrated that scavenging activity and total antioxidants from an aqueous extract of papaya leaves were higher than acetone, ethanolic and methanolic extracts. In contrast, flavonoid and proanthocyanidin from aqueous extract were lower when compared to acetone, ethanolic and methanolic extracts. This finding is supported by the works of Zhang (2015) and Butsat and Siriamornpun (2016). This could be due to the moderate polar to non-polar properties of methanol and ethanol which are more favourable to extract phenolics and flavonoid compounds (Asghar *et al.*, 2016). Lower dipole moments of flavonoids and proanthocyanidins will reduce their solubility in water (Tsao, 2010).

The main advantages of water as solvent for extraction process are safe, cheap, accessible and environmentally friendly. Since components migrating from packaging into the food must be safe if ingested, then water could be the safest alternative. Furthermore, water is also very suitable for small-scale food industries that usually lack technical expertise and capital.

The other important aspects to understand in extraction process is sample preparation (fresh or dried sample), extraction time, temperature, and water-to-leaf ratio. Al-Janabi (2010) reported that the extract from dry samples of *Vigna radiata* L. (leaf, stem, and root) was more effective as antibacterial as compared to fresh samples. From the antioxidant point of view, however, Vankar (2008) reported that higher antioxidant properties were found in aqueous extract of fresh rhizomes of *Curcuma longa* as compared to dry rhizomes. This means that the bioactive compounds are affected by the drying process (Abdullah *et al.*, 2012). Therefore, the most suitable drying method should be further explored to achieve the lowest possibility of quantitative and qualitative losses.

A study by Vuong *et al.* (2013) demonstrated that polyphenol yield increased when the extraction temperature was increased from 50 to 70°C, but decreased when the temperature was further increased to 100°C. In other cases, the extraction process may need higher extraction temperature to extract targeted compound. Vuong *et al.* (2015) further demonstrated that the highest saponin content was obtained at 85°C for 25 min at a water-to-leaf ratio 100:1 mL/g. However, the impact of this setting was the decomposition of the other bioactive compounds. Romasi *et al.* (2011) found that heating time and temperature used in the extraction process of papaya leaves have been shown to have a significant influence on the diameter of the inhibition zone against *Listeria monocytogenes* and *Pseudomonas* sp., while there was no significant effect against *Bacillus stearothermophilus* and *Escherichia coli*. Therefore, many parameters should be carefully considered to target for certain bioactive compounds.

Antimicrobial activity of papaya leaves extract

The presence of bioactive compounds in the papaya leaves extract has been reviewed to have a broad spectrum to inhibit the growth of undesirable microorganisms. As reported by Nirosha and Mangalanayaki (2013), ethanolic and ethyl acetate extracts of papaya leaves at all concentrations used (100, 150, 200, 250 mg/mL) could inhibit the growth of all bacteria tested, while none of them were inhibited by water extract at all concentrations. This could be due to the fact that water extract contained alkaloids, while ethanolic and ethyl acetate extracts contained alkaloids, saponin, glycosides and flavonoids.

This result is similar to a study performed by Ifesan *et al.* (2013) in which ethanolic extract of papaya leaves at a concentration of 0.1 mg/mL inhibited all microorganisms tested, i.e., *Acinetobacter* spp. (6 mm), *Bacillus cereus* (5 mm), *E. coli* (4 mm), *Shigella dysenteriae* (6 mm), *Staphylococcus aureus* (5 mm), *Salmonella Typhi* (4 mm), *Aspergillus niger* (10 mm), and *Aspergillus flavus* (10 mm). On the other hand, water extract only inhibited *B. cereus*, *S. dysenteriae*, and *S. Typhi* at inhibition zone range of 4 to 10 mm. In comparison to other organic solvents, Aruljothi *et al.* (2014) revealed that methanol and acetone had higher antibacterial activity than the aqueous extract of papaya leaves. Orhue and Momoh (2013) demonstrated that there was no significant difference on the minimum inhibitory concentration (MIC) of water, acetone, and ethanolic extracts of papaya leaves against *S. aureus*, *E. coli*, and *Pseudomonas aeruginosa*. Ishiwu *et al.* (2014) also revealed that higher concentration of papaya leaves extract used had a significant reduction on *E. coli* from 65 CFU/mL to 13 CFU/mL, while *S. aureus* was completely inhibited.

The inhibition of microbial growth is due to diverse bioactive compounds. Gyawali and Ibrahim (2014) stated that many phenolic compounds undertake their antibacterial mechanism specifically on the cytoplasmic membrane of bacterial cells, which is particularly associated with the number and position of hydroxyl groups. Potential membrane alteration is an indication that the integrity of bacterial membranes has been disrupted and followed by the entry of more antibacterial agents (Char *et al.*, 2010). Nohynek *et al.* (2006) investigated the ability of phenolic compounds of cloudberry and raspberry extracts in disrupting intracellular membrane of *Salmonella* which is indicated by increased absorption of 1-N-phenylnaphthylamine and release of [^{14}C]galactose-lipopolysaccharide.

Tannin has also been reviewed as one of the potential antimicrobial compounds from the phenolic group. Al-Maliki (2012) demonstrated that tannin isolated from *Ficus carica* leaves was effective to inhibit *S. aureus* (11 mm of inhibition zone) at a concentration of 25 mg/mL, and *Proteus mirabilis* (8 mm of inhibition zone) at a concentration of 90 mg/mL. Three hypotheses on the mode of antimicrobial action of tannins are (i) inhibition of enzyme activity through complexation with substrates of bacteria and fungi, (ii) inhibition of oxidative phosphorylation which contributes to the microbial metabolism, and (iii) complexation of tannin with metabolic ions which will decrease the availability of essential ions for microbial metabolism (Scalbert, 1991; Rebecca *et al.*, 2002). A proteomic approach is also developed to identify an interaction between tannin and functional protein which forms tannin-protein complex, for instance, tannin binds to proline-rich proteins thereby affecting protein synthesis (Shimada, 2006).

Another compound from the phenolic group, flavonoid, causes bacterial cell death through the disruption of the cytoplasmic membrane which leads to the loss of potential membrane and interferes with metabolic activity such as synthesis of DNA, RNA and proteins (Dzoyem *et al.*, 2013). A research conducted by Wu *et al.* (2013) further explored that the activity of the flavonoid compounds can be related to high molecular hydrophobicity and high positive charges on C atom at position 3. In the same mechanism, saponin also disrupts bacterial cell membrane; but the main target is lipid A, part of lipopolysaccharides (by forming lipid A-saponin complex), which then increases the permeability of the bacterial cell wall outer membrane. This mechanism provides a pathway for antimicrobial compounds to penetrate the bacterial cells (Arabski *et al.*, 2009).

In addition to the phenolic groups, the other groups such as carpaine, pseudocarpaine, dehydrocarpaine I, and dehydrocarpaine II (Khuzhaev and Aripova, 2000; Julianti *et al.*, 2014) are alkaloids found in papaya leaves extract. Dhamgaye *et al.* (2014) found that alkaloids have the potential as an anti-*Candida* agent. Treatment of alkaloid Berberine alone could affect the cell wall integrity and dysfunctional mitochondria. A study conducted by Manosalva *et al.* (2016) concluded that alkaloid Berberine presents antibacterial activity against Gram-positive bacterial strains. A study by Handayani *et al.* (2014) reported that crude alkaloid extract from papaya leaves inhibited the growth of *S. aureus*, and also acted in controlling staphylococcal enterotoxin A (SEA) gene-carrying *S. aureus* by suppressing the expression of the SEA gene. Another mode of action of alkaloid is through the binding of the DNA by partial intercalation but depends on the base pair heterogeneity in DNA conformation, in which the non-cooperative binding usually results from DNA with high AT or GC sequences (Bhadra *et al.*, 2008).

Antioxidant activity of papaya leaves extract

Diverse bioactive compounds in papaya leaves extract have been reported to possess antioxidant activity. Each bioactive compound has different antioxidant activities depending on many factors, which are mainly affected by their phytochemical content. As reviewed by Skrovankova *et al.* (2015); cultivar, growing location, cultivation techniques, maturation, processing, and storage (time and temperature) affect the phenolic compounds of blueberry. Furthermore, the phenolic compounds extracted with water solvent showed low antioxidant activity than that extracted with ethanol and methanol solvents (Turkmen *et al.*, 2006). This means that the extraction technique is also a critical part.

As described by Tewari *et al.* (2014), the highest reducing antioxidant power (Fe^{3+} to Fe^{2+}) was obtained from the methanolic extract of papaya leaves, followed by ethyl acetate, ethanolic, and chloroform extracts. Reducing power increases with increasing extract concentrations. On the other hand, a work performed by Ifesan *et al.* (2013) showed that the hexane extract of papaya leaves possessed highest DPPH free radical scavenging activity as compared to ethanol and water, in which both have identical level of activity.

Asghar *et al.* (2016) also found that papaya leaves extracted with ethanol had the highest DPPH free radical scavenging activity, followed by methanol and water solvents. Reducing power of ethanolic extract and water extract were comparable, while extracts with methanol, hexane, dichloromethane, butanol, and ethyl acetate solvents were lower than both extracts. Highest inhibition percentage of linoleic acid was observed on ethanolic extract of papaya leaves, followed by methanolic extract, while aqueous extract was below than both extracts. This result is supported by Mandal *et al.* (2015) who demonstrated that methanolic extract of papaya leaves had higher DPPH antioxidant activity than aqueous extract. This is in contrast to Vuong *et al.* (2013) who found that free radical scavenging activity and total antioxidant obtained from the aqueous extract of papaya leaves were the highest results as compared to acetone, ethanolic, and methanolic extracts.

Several studies have linked antioxidant activity with total phenolic content at positive correlation (Hung and Duy, 2012; Vuong *et al.*, 2013; Pham *et al.*, 2015; Asghar *et al.*, 2016), while the others found negative correlation (Ifesan *et al.*, 2013; Pontis *et al.*, 2014; Aziz and Jack, 2015). The lower the molecular weight of phenolic compounds, the higher the scavenging activity of the DPPH radicals (Paixão *et al.*, 2007). The different solvent and extraction methods used may also influence the type of extracted compounds; so the antioxidant activity obtained can also be different.

The mode of action of phenolic compounds as an antioxidant is through metal chelation that can reduce the rate of Fenton reaction (Tsao, 2010). The product of such reaction is a hydroxyl radical, which is produced when the H_2O_2 comes into contact with a transition metal especially Fe^{2+} and Cu^{+}. It has a single unpaired electron, so it can react with oxygen in triplet ground state (Sharma *et al.*, 2012). Therefore, phenolic compounds that have hydroxyl groups (-OH) in their aromatic ring will donate an electron to the reactive oxygen species such as hydroxyl radical, neutralise their potentially damaging chain reactions, and form stable phenolic radical products in the process (Tsao, 2010; Visioli *et al.*, 2011).

Gülçin *et al.* (2010) reported that tannic acid inhibited lipid peroxidation of linoleic acid emulsion at a concentration of 15 µg/mL. Also, tannic acid acted effectively in various antioxidant assays including DPPH scavenging, ABTS radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, ferric reducing power, and metal chelating on ferrous ions activities. Nevertheless, further investigation on the antioxidant mechanism of tannic acid is needed due to the emergence of its contrary effects. For instance, tannic acid acts as a prooxidant that promotes DNA damage when copper ions are presence in the system, but on the other hand, tannic acid can be used as the powerful antioxidant against the H_2O_2 action and hydroxyl radical formation (Andrade Jr. *et al.*, 2005; Labieniec and Gabryelak, 2005).

Further, Sadik *et al.* (2003) observed the potential inhibition of flavonoid on the peroxidation of linoleic acid catalysed by rabbit reticulocyte 15-LOX1 (15-lipoxygenase 1). Flavone and flavanol aglycones are now being discussed as the potential inhibitors and its influence in enzyme activity in three different pathways, i.e., slowing down the prolongation of the initial lag phase during the accumulation of lipid hydroperoxides, decreasing the peroxidation rate to reach maximum condition during the continuous phase of hydroperoxide accumulation, and the combined action of the flavonoid and intermediates of the catalytic cycle that will inactivate the enzyme in a third phase. However, due to the presence of Fe^{3+} (iron-flavonoid chelation), the inhibition is insensitive, but it is more powerful with flavones and flavonols which possess a catechol group either on the A or B ring as a determinant of radical scavenging efficiency. So, it could mean that the effectiveness of phytochemical compounds as antioxidant is associated with their metal ion-chelating activity. Despite the level of antioxidant activities of papaya leaves extract being found to be varied, in a similar type of compounds, it may have similar action.

Trends in the development of active packaging

Active packaging system is designed in the form of releasing or absorbing a compound (Sivertsvik, 2007), or in other forms based on the active substance used. Ozdemir and Floros (2004) summarised the existing active packaging systems including oxygen scavengers, carbon dioxide absorbers / emitters, moisture absorbers, ethylene scavengers, ethanol emitters, antimicrobial or antioxidant releasing films, flavour-absorbing or releasing films, and others. Active packaging system involves the interaction between the active substances in the packaging with food matrix to prolong the shelf life of packed products by giving desirable properties. For example, the addition of antimicrobial agent into the packaging materials that interacts with each other in order to decrease, inhibit, or retard the growth rate of the pathogens and/or spoilage microorganisms (Suppakul *et al.*, 2008).

Quintavalla and Vicini (2002) and Han (2003) illustrated the schematic representation of antimicrobial food packaging systems. In the first model, an antimicrobial agent is incorporated into the packaging system in a single layer and will be released into the food matrix gradually. The second model is almost similar to the first model, but with an inner layer as a controller in releasing the antimicrobial agent. In the third model, a formulation containing an antimicrobial agent is incorporated into a layer of packaging material. The final model describes an immobilized antimicrobial agent which will be activated only when microorganisms come into contact with the surface of the packaging material. In addition, the addition of an antioxidant agent into the packaging material by using existing schematics may have similar interaction but in a different mode of action, depending on its function. However, the solubility of active substances should be confirmed with the packaging materials and the food wrapped. This factor relates to the migration rate of active substance and their effectiveness (Bastarrachea *et al.*, 2011).

In recent years, many investigations have been conducted to develop an active packaging system for various food products. Active packaging products have also been largely commercialized. This impacts on the global market of active and intelligent packaging merged with controlled/modified atmosphere packaging (CAP/MAP) for the food and beverages packaging which increased from $15.5 billion in 2005 to $16.9 billion in 2008, and is expected to attain $23.6 billion in 2013 (Restuccia *et al.*, 2010). In the United States and the Asia-Pacific region, the active packaging has successfully developed in many food products.

Conversely, in Europe, the development of active packaging is not as faster as in those countries. The most likely reasons for this are restrictions by the authority, lack of awareness on acceptability to European consumers, the advantage of such systems, and the financial and environmental impacts (Silvestre *et al.*, 2011). Furthermore, GTAI (2018) reported that plastic demand in the European market reached 46 million tons per year, and plastic consumption contributed to one-fifth of total global plastic consumption. These conditions make the European market as one of the biggest plastic markets in the world. This supports the reason why the current trend in Europe is not active packaging, but the bio-based plastic, because the environmental concern is considerably voiced.

WEC (2016) predicted that (i) plastic production would increase from 311 million tons in 2014 to 1,124 million tons in 2015, (ii) the ratio of plastics to fish in the ocean (by weight) would increase from 1:5 to more than 1:1, (iii) global oil consumption would increase from 6% to 20%, and (iv) plastic share of carbon budget would increase from 1% to 15%. Of course, this is a warning for the packaging industries to reduce the use of conventional plastics which are non-biodegradable such as low-density and high-density polyethylene (LDPE and HDPE), polypropylene, polystyrene, polyvinyl chloride (PVC), and polyethylene terephthalate (PET). Moreover, the application of active packaging using those polymers as much as possible should be avoided. However, this statement does not rule out the possibility of application of active substances in these polymers, because this is not solely about environmental impact, but also considering the food wrapped, protectability level, convenience, and cost-effectivity.

Bioplastics belong to either or both categories of bio-based plastics and biodegradable plastics. Tokiwa *et al.* (2009) illustrated the category of bioplastics in understandable comparison. Bio-based plastics but non-biodegradable may still cause environmental concern as compared to the biodegradable one. In response to the case, the application of active substances in the biodegradable polymers from biomass or renewable resources (biodegradable active packaging) is an advisable strategy due to its properties and the current needs.

Mekonnen *et al.* (2013) described the biodegradable polymers made from renewable resources, i.e., starch-based (corn or potato), cellulosics-based (cellulose acetate), protein-based (soy or animal protein), microorganism-based (polyhydroxyalkanoates (PHA)), and biotechnology-based (polylactic acids (PLA)). Their uses as the biodegradable active packaging are summarised in Table 2. Many active substances can improve their antimicrobial and/or antioxidant properties of these biodegradable polymers but typically reduce mechanical resistance and barrier properties. Hence, the combination of two or more different polymers with mutual interaction is possible in all formulations.

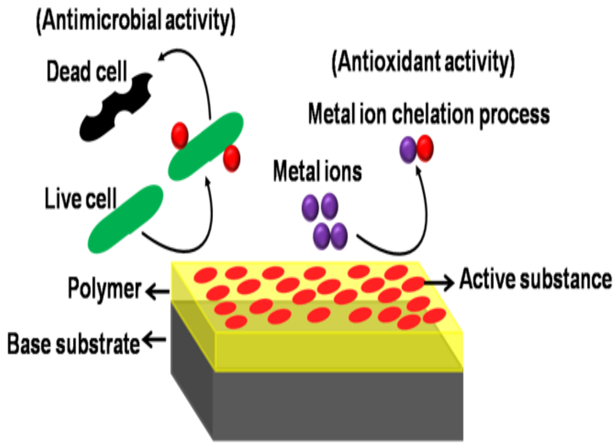

Figure 1. An active substance with antimicrobial and antioxidant activities.

Extract of papaya leaves as an active substance in the food packaging

Due to antimicrobial and antioxidant activities of papaya leaves extracts as previously reviewed, its application in the active food packaging can therefore be a new insight. Nevertheless, studies about the extract of papaya leaves as an active substance in the active packaging system are still very rare; therefore can be an opportunity for further investigation. Its application in the active packaging system may be categorised as the antimicrobial and antioxidant-releasing agent, or in other words, they act as a double agent. Figure 1 illustrates how this active substance works.

One research about the application of papaya leaves extract in the active packaging sector has been carried out by Yehuala and Emire (2013). They

Table 2. Studies about the development of biodegradable active packaging.

Matrix system	Active substance and / or reinforcement	Type of active packaging system	Characteristic	Reference
Polylactic acid (PLA)	Nisin	Antimicrobial releasing	Films made from PLA and nisin had better inhibition to the growth of Listeria monocytogenes in liquid egg white at 24°C, *Escherichia coli* O157:H7 in orange juice at 24°C, and *Salmonella* Enteritidis in liquid egg white at 4 and 24°C, as compared to control (inoculated medium without a film) and PLA films.	Jin and Zhang (2008)
Polylactic acid (PLA) + Polyhydroxybutyrate (PHB) blends	Catechin (CAT), acetyl tributyl citrate (ATBC)	Antioxidant releasing	The incorporation of catechin improved thermal stability (PLA-PHB-CAT-ATBC blends). Its incorporation also increased elastic modulus and hardness as compared to the mixtures without catechin.	Arrieta *et al.* (2014)
Polylactic acid (PLA) + Poly(trimethylene carbonate) (PTMC)	Oregano essential oil (OEO)	Antimicrobial and antioxidant releasing	Films treated with the combination of OEO at all concentrations increased the antioxidant and antimicrobial activities. The higher of OEO concentration used, the higher activities were observed, but the higher of water vapor permeability. About 9% of OEO concentration was suggested into the blends.	Liu *et al.* (2016)
Mixed flour (cassava, rice, and waxy rice flours) / thermoplastic flour (TPF)	Eugenol, Chitosan nanoparticles	Antioxidant releasing	The decrease in tensile strength, modulus, and elongation at break of TPF were observed due to the incorporation of 3% of eugenol-loaded chitosan nanoparticles but the antioxidant activity and water vapor permeability were improved. Furthermore, radical scavenging activity and reducing power of TPF containing eugenol-loaded chitosan nanoparticles were higher compared to free eugenol-containing TPF.	Woranuch and Yoksan (2013)
Cassava bagasse + Polyvinyl alcohol (PVA)	Clove essential oil (CEO) and oregano essential oil (OEO)	Antimicrobial releasing	Foam trays with the combination of OEO had higher antimicrobial activity than trays with CEO. The addition of OEO increased the strain at break but reduced the stress at break. This treatment also decreased water absorption and adsorption capacities.	Debiagi *et al.* (2014)
Corn starch + Polyvinyl alcohol (PVA)	Citric acid, glutaraldehyde, Grewia optiva fibres	Antibacterial releasing	Tensile strength with cellulosic fibres increased tensile strength, degree of swelling, and biodegradability. Starch-PVA crosslinked blend film and fibre reinforced blend film had antibacterial activity against *Staphylococcus aureus* and *E. coli* in fair differences.	Priya *et al.* (2014)
Bovine-hide gelatin (G) in combination with or without chitosan (Ch)	Clove (Cl)	Antimicrobial releasing	G and G-Ch films had no antibacterial activity, while G-Cl and G-Ch-Cl films exhibited antibacterial activity. The matrix used (G or G-Ch) did not reduce the efficacy of Cl as an antibacterial agent. However, the water solubility of G-Ch-Cl film was better than G-Cl film.	Gómez-Estaca *et al.* (2010)
Soy protein isolate (SPI)	Grape seed extract (GSE), nisin, EDTA	Antimicrobial releasing	SPI film made with the combination of GSE, nisin, and EDTA was more effective against *L. monocytogenes*, *E. coli* O157:H7, and *S. typhimurium*, as compared to another combination of antimicrobial agents. On the other hand, the highest thickness, puncture strength, and tensile strength were observed at SPI film containing GSE only.	Sivarooban *et al.* (2008)

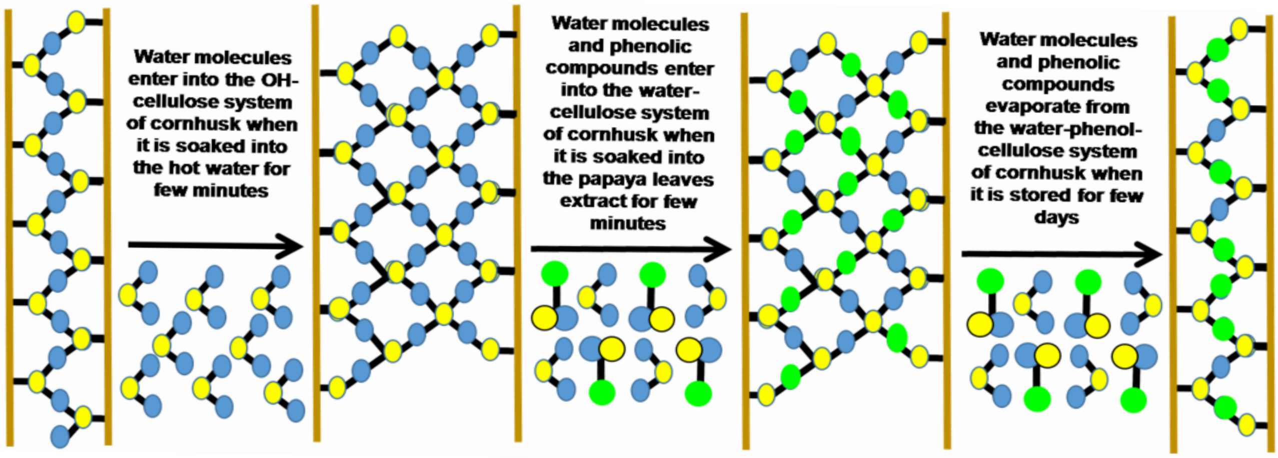

Figure 2. The proposed mechanism of incorporation of papaya leaves extract into the dried cornhusk. Brown line = cellulose; blue circle = hydrogen; yellow circle = oxygen; and green circle = phenol ring.

reported that films made from a mixture of 70% of *Aloe debrana* extract, 30% of papaya leave extract, and in combination with various concentrations of glycerol and gelatine exhibited inhibitory zones against all microorganisms tested. Further, their research explained that *E. coli* and *Candida albicans* were sensitive toward *Aloe debrana* extract, whereas the other microorganisms were sensitive toward papaya leaves extract. These results indicate that both extracts can synergise with each other.

Wahyuningsih *et al.* (2016) explored the application of cornhusk packaging (biodegradable traditional packaging) by soaking for a few minutes. In Indonesia, cornhusk is used as packaging for IMF (Intermediate Moisture Food) products such as *dodol* and *wajik*. In the work, 25 mg/mL of saponin extract from papaya leaves was incorporated into the dried cornhusk and showed the lowest number of total plate count and total yeast and mould count, while 25 mg/mL of saponin crude extract exhibited the lowest WVTR value. This result indicates that those extracts can be incorporated in the dried cornhusk while providing excellent effects. However, their study does not tell us how the papaya leaves extract can be incorporated into the dried cornhusk. Hence, this review offers the proposed mechanism about the incorporation of papaya leaves extract into the dried cornhusk, as illustrated in Figure 2. The extract can interact with water-cellulose system of the cornhusk, because in their study, the papaya leaves were extracted with ethanol:water solvent. This is important to note that solvent types play a role in this incorporation system.

Matan *et al.* (2011) also studied the application of active substance in the biodegradable traditional packaging (*Areca* palm leaf sheath). In Thailand, this leaf sheath is commonly used to wrap durian paste and dried fish. By dipping the *Areca* palm leaf sheath into the essential oils (cinnamon, clove, anise, and peppermint), the antifungal activities of leaf sheath were observed, in which cinnamon oil was the strongest inhibitory agent. That is why papaya leaves extract may also be applicable as an antifungal for this traditional packaging. Also, this statement does not rule out the possibility that this extract can be applied to the other biodegradable-based packaging.

From another point of view, papaya leaves extract can also be applied as an edible active coatings, for example the coating for poultry meat and egg, ruminant meat, fruits, and vegetables. Application on these food products is directed to improve product safety because foodborne outbreaks increased during 2009-2016. In 2016, *Salmonella* Oranienburg strain in the eggshells, *E. coli* O157:H7 in the beef products and *Listeria monocytogenes* in the frozen vegetables were still reported frequently (CDC, 2016). Many opportunities in which papaya leaves extract can be widely used for developing the potency of active packaging and its combination with other active substances are recommendable.

Conclusion

Papaya leaves extract is one of the powerful antimicrobial and antioxidant agents due to its content of phenolic and non-phenolic compounds. With respect to conventional extraction methods, ethanol, water, or their mixtures, can be used as an extraction solvent to attain high quality and quantity of papaya leaves extract. A dry sample can also be suggested to ease the extraction process regardless of the targeted compounds because they can be optimised using extraction time and temperature. Owing to the need for a safe, remarkable, and low-cost active substance in the food packaging, papaya leaves extract can be incorporated into the biodegradable active packaging, bio-based films, edible active coating, and other packaging systems. The incorporation can be done by spraying, soaking, dipping, or direct mixing into the formulation of packaging after looking at the material and system of packaging used. Further, it is possible to combine papaya leaves extract with two or more active substances such as essential oils to exhibit synergistic effects.

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