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Therapeutic Potential of Rubber Latex: A Review

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ABSTRACT

Exploration of the constituents of rubber for medicinal application is very limited due to the concern of allergenicity. However, the recent discovery of the ability of latex sera to exert specific antiproliferative activity against cancer-origin cell lines has paved a light of utilising rubber latex as therapeutics. Rubber latex and its seed oil show many potentials in various biological activities such as antifungal, antioxidant, anti-melanogenesis as well as a biomaterial in relation to angiogenesis. This review describes the current scientifically reported progress on the potential use of rubber in the field of medical research plus positive side concerning latex allergenicity.

Key words: Allergen, *Hevea brasiliensis*, Natural rubber latex.

Hevea brasiliensis is well-known to produce raw material in the form of rubberwood and latex which has been exploited significantly in downstream of rubber-based industries (Lee and Wendy, 2017). The latex is easily collected by tapping the trunk before coagulated and processed into cured rubber. The harvest is then exported under five products sectors namely tyres & inner tube, footwear, latex products, industrial rubber goods and general rubber goods (Fig 1) with a value of RM11,297.16 million in 2018 (Malaysian Rubber Board, 2018).

The rubber tree is categorized under genus *Hevea* and family of Euphorbiaceae. Commonly, this tree referred to as 'sharinga tree', 'jebe', 'seringueira', 'seringueira-rosada', seringueira-verdadeira' in Spanish meanwhile the Italian call it as 'della gomma'. In Malaysian, it is typically called 'pokok getah' (Florence and Fashorant, 2018). Under this genus, only *H. brasiliensis*, *H. guianensis* and *H. benthamiana* can produce usable rubber as other species have a too high ratio of resin to rubber (Mekonnen, 2015; Florence and Fashorant, 2018). Out of the three, only *H. brasiliensis* are planted commercially (Florence and Fashorant, 2018). It originates from South America and later introduced to Asian countries during British rule (Hagan *et al.*, 2005). In Malaysia, rubber tree was planted after Sir Henry Wickam brought rubber seed from Brazil in 1876 through Kew garden (Dijkman, 1951).

Despite being of important economic player, surprisingly rubber latex has no reference of use in folk medicine (Duke and Wain, 1981). In the healthcare sector, latex use is limited to the production of the condom, gloves, urinary catheters, dental dams and breathing bags for anaesthesia (Rubio, 2006). Exploration of the medicinal property of rubber is hardly discussed, thus this review compiles researcher's approaches exploring the biological potential of rubber in addition to discernments on latex allergenicity.

Physicochemical composition of rubber

The proximate analysis shows rubber seed contains iron, calcium and phosphorus as high as 6.2, 109 and 429 mg/ 100 g, respectively. In addition, it has a total energy value of 702 kcal/100 g (2,948 kJ/100 g) with the total fat content of 48% (Selle *et al.*, 1983). The seed has a moisture content of 3.99%, the protein content of 17.41 g/100g, the fat content of 68.53 ± 0.04 g/100g and ash content of 3.08 ± 0.01g/ 100g. Rubber seed oil is rich with unsaturated fatty acids with the percentage of 69.22% and the highest fatty acid dominated by oleic acid with an amount of 35.91% followed by linoleic acid bearing percentage of 33.31% (Chaikul *et al.*, 2017). In terms of protein composition, the most abundant amino acid in rubber seed is glutamic acid (16.13%) and cysteine (0.78%) is found to be the lowest (Eka *et al.*, 2010).

As the seed is a rich source of energy, protein and calcium, it was suggested to be included in feed formulations for poultry and livestock (Udo *et al.*, 2016). However, due to the presence of a high concentration of hydrogen cyanide and cyanogenetic glucoside (Eka *et al.*, 2010; Lee and Wendy, 2017), its utilization as feed creates apprehension. The seed of the rubber tree labelled poisonous as it contains 6% of free cyanide and 94% of bound cyanide making the total cyanide content in fresh seed to be approximately 130-230 mg/100 g (Selle *et al.*, 1983). Cyanogenetic glucoside was found as high as 186mg/kg in fresh rubber seed (Eka *et al.*, 2010).

It is necessary to eliminate these two toxic compounds which act as an anti-nutritional compound that prevents utilization of rubber seed as a food source. Currently,

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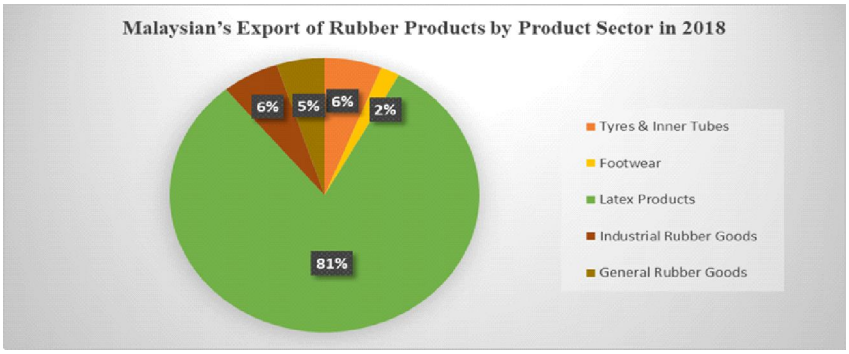


Fig 1: Malaysian's export of rubber products by product sector with a total value of RM 11,297.16 million. (Adapted from Malaysian Rubber Board Annual Report 2018).

the poisonous effect can be eradicated through boiling (Reed, 1976), by roasting at 350°C for 15 minutes (Lee and Wendy, 2017) and also by storing the seeds in dark condition for a minimum period of four months (Fuller, 1988). Indians in the Amazon Valley of South America consumed boiled rubber seed and no adverse effect was reported (Njwe *et al.*, 1988).

H. brasiliensis has been classified as tanniniferous plant due to the high content of tannin in the leaves. It was found that withering of rubber leaves could lower total tannin content yet simultaneously increased content of condensed tannin. Consequently, it was concluded that fresh rubber leaves also could be a source of herbal medicine for ruminants *i.e* goats (Wigati *et al.*, 2014).

Pharmacology of rubber

Antifungal effect

Latex C-serum was shown to exert specific antifungal activity against *Aspergillus niger* while latex B-serum expressed anti-*Candida albicans* activity (Daruliza *et al.*, 2011; Daruliza *et al.*, 2011). The growth of *Trichosporon cutaneum* and *Cryptococcus neoformans* were inhibited with MIC value of 40.615µg/mL and 56.078 µg/mL respectively (Giordani *et al.*, 2002). FTIR analysis has revealed the presence of abundant proteins in C-serum like hevein which were thought to be responsible for plant defence against fungus (Havanapan *et al.*, 2016; Kerche-Silva *et al.*, 2017).

Anti-melanogenesis

The ability of rubber seed oil to inhibit production of melanin was investigated in B16-F10 melanoma cells and it was demonstrated that inhibition of melanogenesis does take place in concentration-dependent manner. Melanin content, tyrosinase and TRP-2 activity were significantly reduced compared to positive control and this outcome was also correlated with oleic and linoleic acid which accelerates the ubiquitin-proteasome pathway. Consequently, the activity of melanogenic enzyme will decline leading to decreased pigment production. This founding creates another approach to employ rubber seed oil as functional raw material in cosmetic products (Chaikul *et al.*, 2017).

Antiparasitic and insecticidal effects

Based on the World Agroforestry Centre, the oil extracted from the rubber seed is an effective treatment against lice and houseflies. The extracted oil was also used to produce illumination (Brücher, 2012). Besides, a mixture of fresh latex and castor oil can be utilized as vermifuge which kills intestinal worms (Rubio, 2006).

Antioxidant effect

Antioxidant property of latex C-serum has been assessed and it was reported that the serum was able to scavenge hydroxyl, hydrogen peroxide and nitric oxide radicals in a dose-dependent manner and its activity resembled that of ascorbic acid (Kerche-Silva *et al.*, 2017). This scavenging activity can be correlated to naturally present antioxidants in rubber latex namely thiols, ascorbate, γ-tocotrienol, phytosterols, phospholipids, phenols, betaines, proteins and amino acids (Musigamart *et al.*, 2014; Zhang *et al.*, 2017). Rubber seed also exhibited a good antioxidant potential by scavenging DPPH radical and ABTS cationic radical (Lourith *et al.*, 2014). This property was further proven when the oil exhibited a higher cellular protective effect in 3T3-L1 cell line compared to hydrogen peroxide-treated group. The cell viability was found to have no significant difference in between untreated, ascorbic acid-treated group and rubber seed oil treated group. Presence of abundant unsaturated fatty acids especially oleic acid and linoleic acid in rubber seed oil are said to be the responsible factor for its antioxidant activity (Chaikul *et al.*, 2017).

Angiogenesis

Angiogenic and wound healing property of rubber latex were investigated using the chick chorioallantoic membrane assay (CAM) and rabbit ear dermal ulcer model respectively. The result indicated that latex could induce vascularization. Moreover, the latex was found to stimulate neovascularization and tissue growth without provoking rejection from the host. Subsequently, the latex was regarded as a potential biomaterial being able to accelerate wound healing in addition to enhance vascular permeability (Balabanian *et al.*, 2006; Ereno *et al.*, 2010; Mendonça *et al.*, 2010; Mrue *et al.*, 2004). A clinical trial conducted on 107 patients suffering

from chronic otitis media, whereby transitory latex was employed to underlay tympanoplasty, revealed that transitory latex had good biocompatibility with tissue of human tympanic membrane and was able to induce greater graft vascularization compared to sylastic® implants. It was also reported that no sign of toxicity or allergy manifestation occurred during the trial(Araujo *et al.*, 2012).

Histological analysis has shown that latex biomembrane was able to produce satisfactory recovery of 60% compared to 20% satisfactory recovery in the control group when natural latex biomembrane with 0.1% polylysine was utilized in conjunctival reconstruction in adult New Zealand rabbits. In addition, an average number of vessels per optical field in surgical wound eyes with biomembranes was double that of the control group, suggesting that conjunctival scarring and neoangiogenesis can be promoted by the biomembrane (Pinho *et al.*, 2004).

As latex has been shown to be a biomaterial with strong angiogenic property, it has been commercialized as a band-aid curative (BIOCURE®) in over 60 countries around the world for the treatment of ulcers in diabetic patients (Frade *et al.*, 2004; Kerche-Silva *et al.*, 2018) and also in pressure ulcers (Frade *et al.*, 2006). The latex was proposed as drug delivery system whereby the membrane polymerized at room temperature (27°C) was shown to release 66% of its BSA content for up to 18 days (Herculano *et al.*, 2009). Other research groups utilize latex as a carrier to deliver nanoparticles, drug and plant extract to various biological targets (Azevedo Borges *et al.*, 2014; Barros *et al.*, 2015; Dias Murbach *et al.*, 2014; Guidelli *et al.*, 2013; Herculano *et al.*, 2011, 2010; Miranda *et al.*, 2018; Suksaeree *et al.*, 2012). For instance, the latex was integrated into a biodevice which would release *S. marginata* extract for chronic wounds healing (Barros *et al.*, 2018).

Cytotoxicity studies

The possibility of using rubber latex as a potential anti-cancer agent was first suggested by Ong and co-workers in 2009. It was discovered that B- and C- sera of rubber latex have selectively reduced the growth of cancer-origin cell line (Hela) after being treated for 48 hours with 8-10 ng/ml of rubber latex extract (Ong *et al.*, 2009). In addition, it was found that latex B- and C- sera exhibited low toxicity level in brine shrimp lethality test (BSLT), with LC_{50} of 461.0 mg/mL and 98.4mg/mL respectively (Daruliza *et al.*, 2011).

Further subfractionation was conducted whereby both B- and C- sera were processed via two different methods namely dialysis and boiling. This generates different subfractions which were B-serum precipitate (BBP), boiled B-serum supernatant (BBS), boiled C-serum precipitate (BCP), boiled C-serum supernatant (BCS), dialysed B-serum precipitate (DBP), dialysed B-serum supernatant (DBS), dialysed C-serum precipitate (DCP) and dialysed C-serum supernatant (DCS) fractions.

It was reported that both latex B- and C- sera were able to elicit specific anti-proliferative activity towards cancer-origin cell lines without affecting the growth of non-cancer-origin cell lines (Havanapan *et al.*, 2016; Kerche-Silva *et al.*, 2017; Sunderasan *et al.*, 2014, 2013). Whole B-serum and its dialyzed fraction DBP were found to be able to eradicate growth of breast cancer-origin cell line *i.e.* MDA –MB-231 with LC_{50} of 85.9 µg/mL and 5.4 µg/mL respectively. On the other hand, latex C-serum and its dialyzed fractions, DCP and DCS, were found to reduce the growth of liver cancer-origin cell line HepG2 with LC_{50} of 889ng/mL, 280 ng/mL and 2 ng/mL respectively (Lam *et al.*, 2012; Sunderasan *et al.*, 2013). According to the National Cancer Institute (NCI), standard IC_{50} values for the substantial anticancer activity should be less than 30 µg/mL in crude extract and this value was determined based on pre-screening results for antitumor agents by treating plant crude extracts against a panel consisting of 60 cancer cell lines (Suffness, 1990). Hence, rubber latex subfraction is suitable for further screening to elucidate its anti-cancer potential.

DNA laddering assay and qRT-PCR analysis have subsequently revealed that cell death induced by latex C-serum was not via the classical apoptosis death signalling pathway (Lam *et al.*, 2012; Sunderasan *et al.*, 2014). This was further validated through Annexin V and propidium iodide labelling of the C-serum treated HepG2, MCF-7 and MDA-MB231 cell lines. Cell cycle analysis using BrdU incorporation showed the treated cells were arrested in the G0/G1 phase compared to the non-treated cells. Later, the cell death mechanism triggered by DCS- and DCP- treated cells was confirmed to be autoschizis and was visualized using SEM and TEM analysis (Sunderasan *et al.*, 2014). As the cellular mechanisms of autoschizis are still not completely defined now, latex C-serum might serve as a biological model to further unlock the cell death mechanisms.

Recently, cell viability guided fractionation of C-serum was performed and it was found that the antiproliferative activity of DCS-F2 and DCS-F3 might due to abundant presence of proteins which include malate dehydrogenase, protease inhibitors, latex cystatin, nucleoside diphosphate kinases and fructose biphosphate aldolase (Lam *et al.*, 2015). *In vivo* studies would be necessary to elucidate the potential of rubber latex sera as an agent in cancer treatment.

Another research group isolated nine compounds from the shell of rubber seed and performed MTT cytotoxicity assay. It was found that only buddlenol A cause growth inhibition with an IC_{50} value of 20.6 µmol/L against B16 melanoma, a murine tumor cell line used as a model for human skin cancers. Out of the nine isolated compounds, isoamericanol A, americanol, buddlenolA, balanophonin and erythro-Guaiacylglycerol-β-O-4-dehydrodisinapyl ether were found to elicit inhibition towards human leukocyte elastase with IC_{50} values of 45.5, 57.6, 115, 168 and 171 µmol/L, respectively (Ren *et al.*, 2012).

Positivity of latex allergenicity

Latex allergenicity is the hottest topic in allergy research and it has been found that fifty-six polypeptides derived from

the latex of *H. brasiliensis* are associated with Ig-E mediated immune response (Brehler and Kütting, 2001). However, apart from causing an allergic reaction to the host, latex allergen is also able to function in a positive manner. For instance, Hev b 13, an allergenic esterase of latex, was shown to possess anti-inflammatory activity by increasing the release of anti-inflammatory cytokines by immune cells and subsequently inhibit the action of pro-inflammatory cytokines to overcome autoimmune response. Specifically, Hev b 13 was found to stimulate the production of IL-10 and TGF-β in a human mononuclear cell with aid of phytohemagglutinin in arthritis and colitis-induced mice. Concurrently, it was demonstrated that TNF-α, IL- 1β and IL- 6 productions were inhibited (L. D. B. Teixeira *et al.*, 2012; L. de B. Teixeira *et al.*, 2012). The ability of Hev b 13 as an anti-inflammatory agent was further proven in rats with experimentally-induced acute sepsis where it caused a significant decline in total and differential leukocytes as well as suppression of TNF-α and IL-6 production, associated with the increase in IL-10 and IL-4 in plasma and lung tissue (Araújo *et al.*, 2017).

Measurement of concentrations of specific allergenic proteins or polypeptides is essential to evaluate the allergenic potential of medical devices made of latex (Palosuo *et al.*, 2007). Four major allergens have been identified (Hev b 1, 3, 5 and 6.02) and these allergens clinically represent total allergenicity of latex (Czuppon *et al.*, 1993; Alenius *et al.*, 1996; Akasawa *et al.*, 1996; Palosuo *et al.*, 2002; Sutherland *et al.*, 2002). These allergens can be set as a platform for diagnostic purpose before rubber-based products being marketed. Identification of these four clinically relevant latex allergens can be done by a skin prick test (SPT)-validated IgE ELISA inhibition (Palosuo *et al.*, 1998) and the present capture EIA allergen sum test. Presently, investigation towards the application of latex in medical devices with zero allergenicity is in focus. A good example would be the preparation of hydrogel from deproteinized natural rubber latex (DNRL) with gelatinized starch as wound dressing (Kleawkla, 2018).

CONCLUSION

In sum, the contribution of rubber in the medicinal field appears to be promising. Currently, it has been shown that it has high potential to be applied majorly in cancer treatment and in cosmetic science. The content of allergen in rubber latex was a concern previously, however with current advanced technology, the issue of latex allergenicity can be eradicated and/or modified for use in medical treatment. Similarly, a better scientific approach should be taken to eradicate hydrogen cyanide and cyanogenetic glucoside for complete utilization of other beneficial components found in the rubber seed.

Conflict of interest

The authors declare there is no conflict of interest.

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