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A COMPREHENSIVE REVIEW ON ANTI-CANCER PROPERTIES AND MEDICINAL VALUES OF ARTOCARPUS HETEROPHYLLUS

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ABSTRACT*:* Research is focusing on the search for new types of natural chemotherapeutic agents derived from plants which are proving to be excellent sources of new compounds. This review aimed to highlight the information regarding physicochemical properties, Chemical Composition, Anticancer properties and their administrations of jackfruit. Artocarpus heterophyllus shows anticancer properties due to the presence of phytochemicals like lignans, saponins, flavonoids carotenoids, tannins, volatile acid steroids and also the properties such as anti-oxidant, anthelminthic, anti-inflammatory, anti-bacterial, anti-viral activities. The phytochemical constituent artocarpine have effect on cancer cells. Target specific agents that are capable of inducing selective apoptosis of cancer cells but are harmless to the normal cells are receiving considerable attention in the field of cancer prevention and therapy. The flavonoid compound artonine B have anti-cancerous effect on human cancer cells. Different studies are performed on this topic and reported. Also, further researches and studies are ongoing.

OBJECTIVE: The objective of this article is to provide a detailed and systematic knowledge on the anti-cancer property of Artocarpus heterophyllus (jack fruit) and its medicinal values.

METHODS: A vigorous, maximum sensitive and online search of the literature was performed in published articles in the last 20 years (JUNE 2000–JUNE 2020). The databases searched were MEDLINE (via PubMed) and Cochrane Library.

CONCLUSION: Cancer is becoming a high profile disease in developed and developing worlds. In 2017 the WHO published that in 2015, 7.6 million people died from cancer related diseases with the majority of these people living in low-income countries. the demand for a cure and the prevention of cancer is extremely high. Experimental studies performed in the past suggest that, jackfruit possesses diverse medicinal uses including antioxidant, anti-inflammatory, antimicrobial, ant cariogenic, antineoplastic and hypoglycemic effects, inhibits melanin biosynthesis, possesses wound healing properties, and causes a transient decrease in the sexual performance. Target specific agents that are capable of inducing selective apoptosis of cancer cells, but are harmless to normal cells are receiving considerable attention in the fields of cancer prevention and therapy. Therefore, Artocarpus heterophyllus is a candidate for development as a Chemo preventive agent.

IMPORTANCE

Research is focusing on the search for new types of natural chemotherapeutic agents derived from plants which are proving to be excellent sources of new compounds. This review aimed to highlight the information regarding physicochemical properties, Chemical Composition, Anticancer properties and their administrations of jackfruit. Artocarpus heterophyllus shows anticancer properties due to the presence of phytochemicals like lignans, saponins, flavonoids carotenoids, tannins, volatile acid steroids and also the properties such as anti-oxidant, anthelminthic, anti-inflammatory, anti-bacterial, anti-viral activities. The phytochemical constituent artocarpine have effect on cancer cells. Target specific agents that are capable of inducing selective apoptosis of cancer cells but are harmless to the normal cells are receiving considerable attention in the field of cancer prevention and therapy. The flavonoid compound artonine B have anti-cancerous effect on human cancer cells. Different studies are performed on this topic and reported. Also, further researches and studies are ongoing.

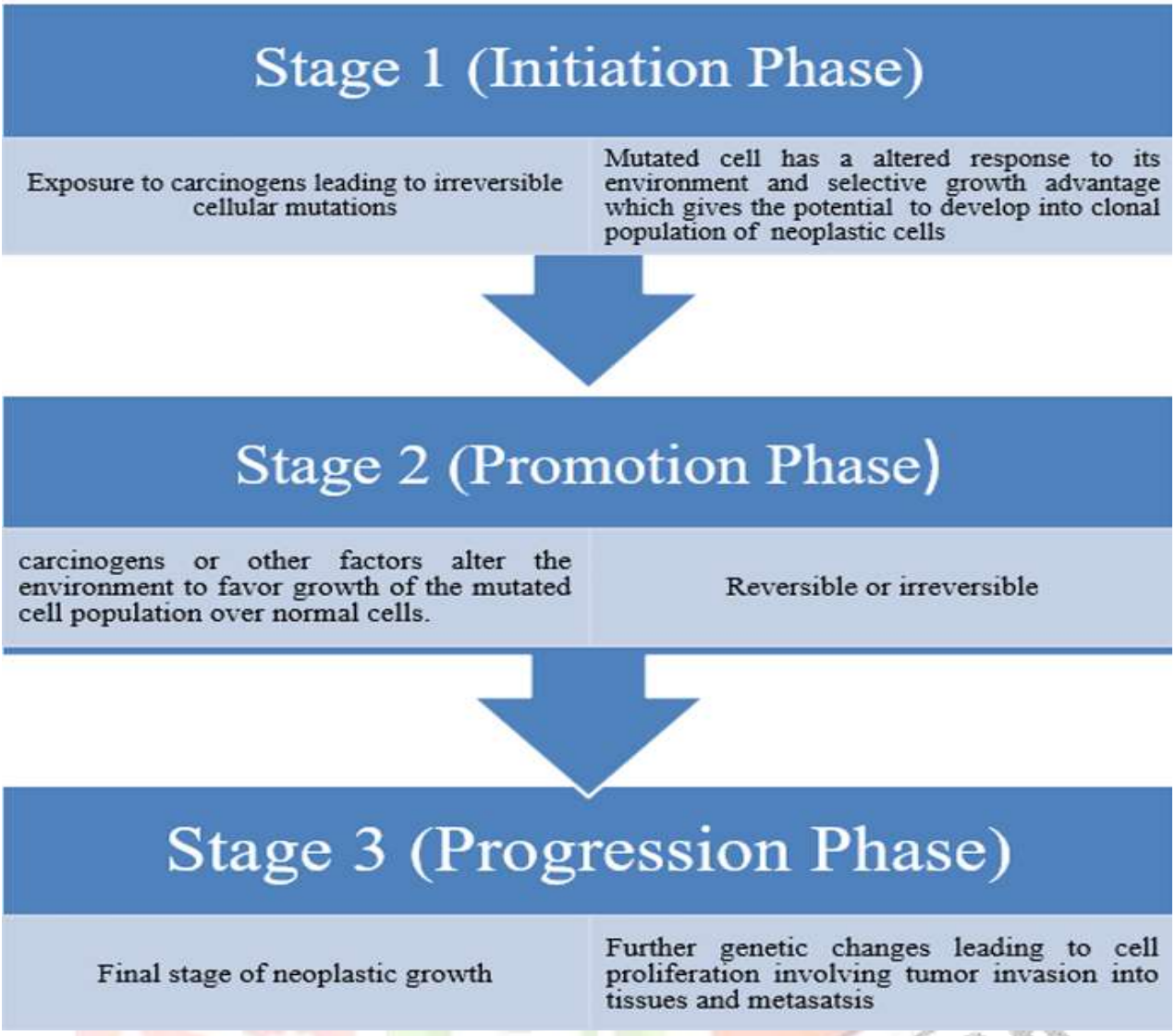
INTRODUCTION

Globally cancer is a disease which severely effects the human population. There is a constant demand for new therapies to treat and prevent this life-threatening disease. The Plant Kingdom produces naturally occurring secondary metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. New technologies include Nano-particles for Nano-medicines which aim to enhance anticancer activities of plant-derived drugs by controlling the release of the compound and investigating new methods for administration. This review discusses the demand for naturally-derived compounds from medicinal plants and their properties.

Cancer is a group of more than 100 different diseases that are characterized by uncontrolled cellular growth, local tissue invasion, and distant metastases. Cancer cells do not respond to the normal processes that regulate cell growth, proliferation, and survival, and they cannot carry out the physiologic functions of their normal differentiated (mature) counterparts. Cancer cells are described as poorly differentiated or immature. Other characteristics of cancer cells include their ability to invade adjacent normal tissues and break away from the primary tumor (metastasize) and travel through the blood or lymph to establish new tumors (metastases) at a distant site. Their ability to stimulate the formation of new blood vessels (angiogenesis) and their endless replication potential further contribute to their continued growth and survival [6][7].

Hence Carcinogenesis is a multistep process that includes initiation, promotion, conversion, and progression. The growth of both normal and cancerous cells is genetically controlled by the balance or imbalance of oncogene, proto-oncogene, and tumor suppressor gene protein products. Multiple genetic mutations are required to convert normal cells to cancerous cells.

Fig 1: Phases of carcinogenesis



Many medicinal and food plants contain large amounts of chemical components having broad spectrum of pharmacological activities like anti-cancer, anti-tumor and anti-oxidant activities. The anti-cancer activities are mainly due to flavonoids and Phenolic acids, phenolic diterpenes. Natural products are reportedly beneficial to physiological health. Various flavonoids and non-flavonoids have been reported as showing anti-cancer, anti-tumor and anti-oxidant activities. Artocarpus heterophyllus or Jackfruit (family of Moraceae) is a monoecious evergreen tree that is grown in several tropical countries. It produces a large pear or barrel-shaped fruit that can grow up to 90 cm long, 50 cm thick and having a weight of 20 kg. At times these fruits which contain numerous hard cone-like points may be as heavy as 45 kg in weight, and up to 36 in. in length and 20 in. in diameter. The term jackfruit is derived from the Portuguese word Jaca, which in turn is adopted from the word “Chakka” of Malayalam (a regional Indian language). In India, the trees are found distributed continuously in places where rainfall is high and, sporadically in areas where it is low [4][8].

Artocarpus heterophyllus widely distributed in tropical region and has been used as traditional folk medicine against inflammation, malarial fever and so on. In addition, the function of Artocarpus heterophyllus in human health such as pulp and seed for tonic; root for diarrhea, fever; wood for

muscular contraction; leaves for activating milk in women and animal, anti-syphilis, vermifuge; leaf ash for ulcers and wound.

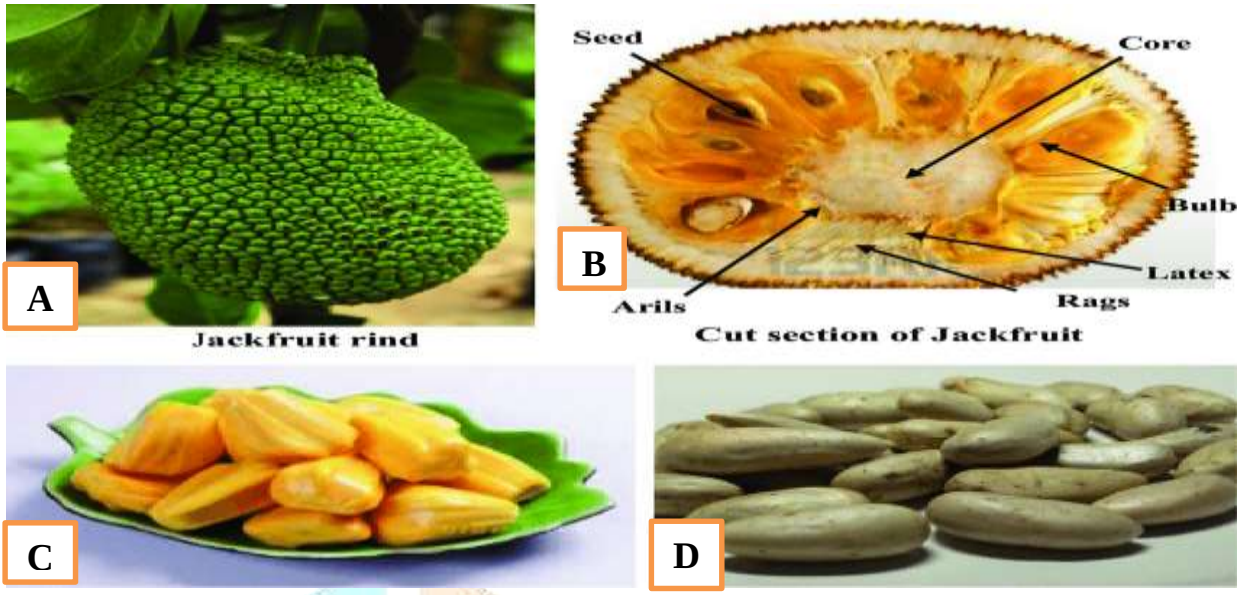


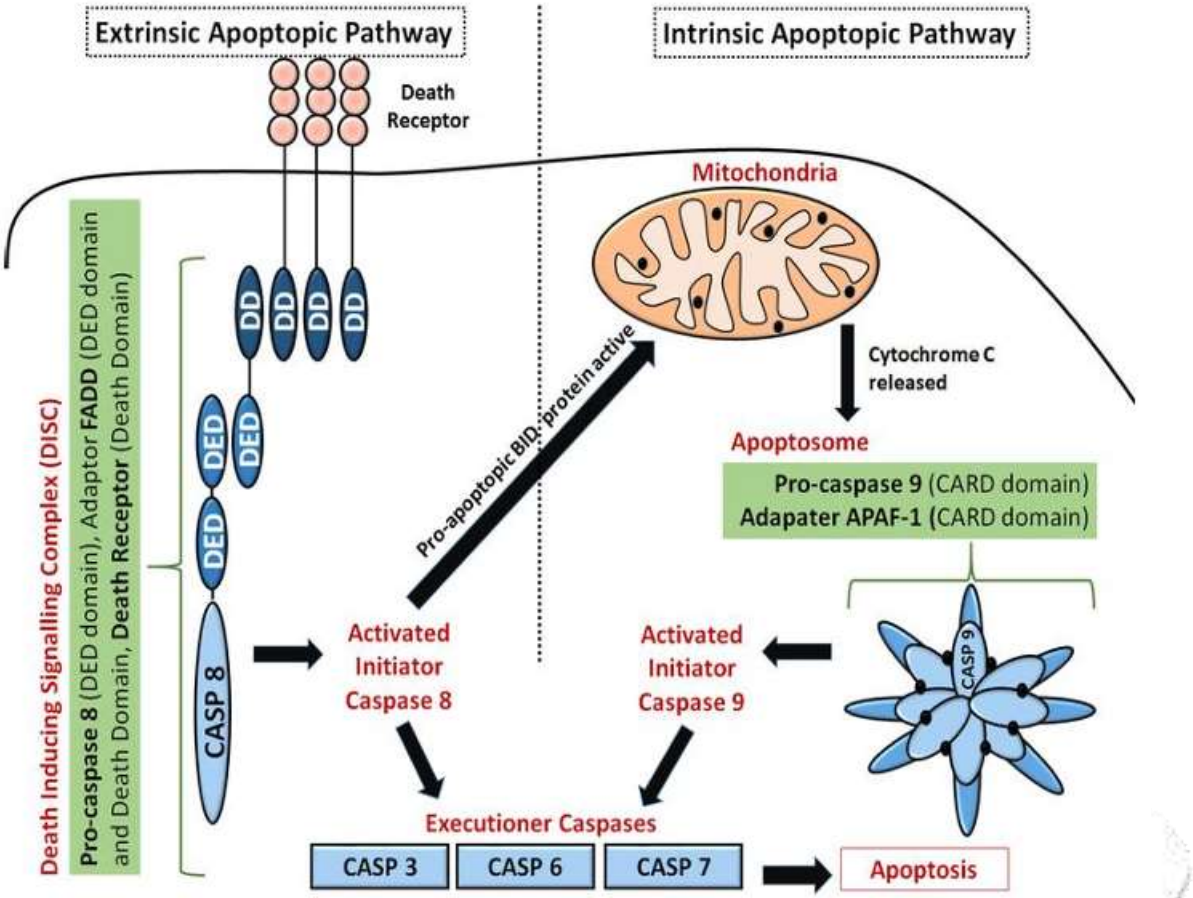
Fig 2: Jackfruit tree with the fruits of different sizes(A), the interior of a ripe jackfruit with the seed(B), pulp of jackfruit(C), and the jackfruit seed(D).

The most common benefits are preventing skin wrinkles, anti-cancer property and promoting digestion. Being a good source of vitamin A, vitamin B, vitamin C and pectin, jackfruit seeds also help in alleviating the pancreatic ailments and aid in blood purification. Vitamin C is vital to the production of collagen; a protein that provides skin with structure and gives firmness and strength. Jacalin, the major protein from the jackfruit seeds has proved as useful tool for the improvement of immune status of patients infected with HIV and Cancer; Bhushan and Z- zaman found its antioxidant and anti-cancer properties. For these medicinal values and efficient ingredients seeds flour has prospectus to be utilized in food manufacturing and marketing.

APOPTOSIS

Apoptosis is a regulated and ubiquitous cellular mechanism in response to pro death signaling. Apoptosis is morphologically characterized by cell shrinkage and condensation, nuclear envelope disassembly, and DNA fragmentation (fig.5). All these changes are due to activation of a cascade of highly specific proteases, called caspases. Within the cascade, caspases can be categorized into two initiator caspase and downstream effectors of apoptosis. Initiator caspases (caspase 2, 8, 9, 10, 11, and 12) are closely coupled to pro-apoptotic signals. Once activated, these caspases are cleaved and activate downstream effector caspases (caspase 3, 6, and 7), which in turn execute apoptosis by cleaving cellular proteins following specific Asp residues [13].

Fig.3: Apoptosis Pathway



Nowadays, there are two well-understood caspase activation pathways. The first is the assembly of the death induced signaling complex (DISC) induced by the binding of the members of the death receptor family including Fas to its ligand. This pathway is also called the extrinsic pathway. The second is the mitochondrial (intrinsic) pathway, which is initiated by the release of cytochrome c from mitochondria to the cytosol, leading to activation of caspase 9 [14] [15].

To understand the mechanism of artocarpine-induced apoptosis of T47D cells, another study investigated the expression level of some protein markers involved in the apoptosis cascade, such as caspase 8 and 10 as markers for the extrinsic pathway, caspase 9 as a marker for the mitochondrial pathway, and caspase 3 as a marker for effector caspase. By immunoblotting analysis, it was detected that cleaved caspase 3, an active form of caspase 3, in the cells. This caspase was observed and gradually increased with increasing concentration of artocarpine. Similarly, the detection of cleaved-caspase 8, a marker for apoptosis via the extrinsic pathway, showed the increased signaling of this protein due to artocarpine treatment. Detection of another extrinsic marker protein, caspase 10, showed that this protein level is reduced due to artocarpine treatment. This might indicate that artocarpine induced apoptosis in T47D cells via the extrinsic pathway. To investigate the possible involvement of the mitochondrial pathway of apoptosis due to artocarpine treatment, a marker for this pathway, caspase 9, was tested; however, the caspase 9 signal was not detected. These results also suggested that artocarpine may induce apoptosis in T47D cells via the extrinsic pathway [15].

Together these observations clearly indicate that the isoprenoid-substituted flavonoids of jackfruit possess cytotoxic effects and that artocarpine is a potential candidate [16].

METHODS

LITERATURE SEARCH

A vigorous, maximum sensitive and online search of the literature was performed using the PubMed, Scopus, MEDLINE and Web of Science Data Bases and Google Scholar. The search strategy was limited to published articles in the last 23 years (JUNE 2000–JUNE 2023) to include the most recent, up-to- date data that reflect the current clinical practice in English. The search terms used were, "Artocarpus Heterophyllus", "Jack Fruit" "Anti-Cancer Properties", "Medicinal values", "Phytochemicals" and "Traditional Medicine" combined with Boolean operators "AND" and "OR" as appropriate.

STUDY SELECTION:

Initial screening of titles and abstracts of the retrieved articles were independently screened by two reviewers to assess their relevance to the review topic. The first stage of screening was performed based on the titles and abstracts. Eligible studies were screened based on the full text in the second stage.

DATA EXTRACTION:

Data extraction was performed by two reviewers using a standardized data extraction. Extracted data included the details such as study characteristics, participant characteristics,

DATA SYNTHESIS: The findings from the synthesized data were performed to find out the Anti-Cancerous properties and the types of phytochemicals present in it and its other medicinal value.

DISCUSSION AND OBSERVATIONS

1. ANTI-CANCER PROPERTY

It is proved that the methanolic extract of Artocarpus heterophyllus had potential cytotoxicity against lung cancer, but non- toxic to the normal cells (HEK293 cell line) as compared to methotrexate. The cytotoxicity of methanolic extract of Artocarpus heterophyllus may be due to the presence of flavonoids having mono to poly phenolic groups in the structure. The flavonoids have reported for their cytotoxic activity due to presence of phenolic groups. The extractive value, total polyphenolic content and anti-cancer activity was at its peak in methanolic extract indicating that most of the active components are extracted with methanol. Cytotoxic changes observed was cell aggregation, cell rounding and cell death. The overall results indicate the promising baseline information for the potential uses of the methanol extracts of tegmen of Artocarpus heterophyllus seed as an anti-cancer agent [1].

2. ANTI-OXIDANT ACTIVITIES

The generation of excess free radicals damages the biomolecules and their prevention is vital for cyto-protective effects. Multiple studies have proved that polyphenols, carotenoids, anthocyanin and flavonoids present in fruits and medicinal plants are reported to be excellent scavengers of the free radicals and to prevent the cellular damage [2][3].

3. ANTI-INFLAMMATORY ACTIVITY

Surfeit generation of free radicals especially under conditions of chronic inflammation is harmful to the cells. The anti-inflammatory properties of phenolic compounds isolated from the ethyl acetate extracts of A. heterophyllus fruits were shown in vitro. Three phenolic compounds were characterized asarto-carpesin [5,7,2′,4′-tetrahydroxy-6-(3-methylbut-3-enyl) flavone], nor-artocarpine (5,7,2′,4′-tetrahydroxyflavone), and ox resveratrol [trans-2,4,3′,5′ tetrahydroxy stilbene] by spectroscopic methods and through comparison with data reported in the literature. The anti-inflammatory properties of the isolated compounds were evaluated by determining their inhibitory effects on the production of pro inflammatory mediators in lipopolysaccharide (LPS) activated RAW 264.7 murine macrophage cells. These three compounds exhibited potent anti-inflammatory Activity [4].

4. ANTHELMINTHIC ACTIVITY

The ethyl acetate ethanol and aqueous extracts of A. heterophyllus seed exhibited significant anthelminthic activity in comparison with the control in vitro. Amongst all the extracts, Ethyl acetate extracts showed a good activity. It indicates that certain non-polar constituents are responsible for the activity. This anthelmintic activity is mainly due to the presence of secondary metabolites namely alkaloids, flavonoids and Triterpenoids extracts of Artocarpus heterophyllus Lam. leaves were evaluated in vitro for their anthelmintic activity [4].

5. INHIBITION OF MELANIN BIOSYNTHESIS

Jack fruit wood extract and the phytochemical artocarpanone was effective and inhibited both mushroom tyrosinase activity and melanin production in B16 melanoma cells. Artoheterophyllin A, artoheterophyllin B, artoheterophyllin C, and artoheterophyllin D isolated from the twigs also possess a tyrosinase inhibitory activity. Study showed the extract of Jack fruit to be one of the strongest inhibitors of tyrosinase activity [9][10].

6. HYPOGLYCEMIC EFFECTS

The extracts of both Artocarpus heterophyllus and Asteracanthuslongifolia Significantly improved glucose tolerance in the normal subjects and the diabetic patients when investigated at oral doses equivalent to 20 g/kg of starting material. With both plant extracts, the dosages used here correspond to those reputed to produce the maximum hypoglycemic effects. Although both extracts had fairly comparable effects on the glucose tolerance of normal individuals, Artocarpus heterophyllus appeared

to be slightly more effective than Asteracanthuslongifolia in diabetic patients. Thus, with diabetic patients, 2 h after the glucose load, the Artocarpus heterophyllus treated group showed a blood glucose level that was 36% less than the corresponding value in the control group while the Asteracanthuslongifolia treated group showed a blood glucose level only 25% less than the corresponding value in the control group [5].

7. ANTI-VIRAL PROPERTIES

Jackfruit lectin (JFL) from A. heterophyllus has been found to have in vitro inhibitory activity with a cytopathic effect toward Herpes simplex virus type HSV-2, Varicella zoster virus (VZS) and Cytomegalovirus (CMV). Several plant lectins have been shown to inhibit infectivity of viruses. For instance, jackfruit has been found to inhibit in vitro infection of HIV-1 without preventing the virus from binding to the host cell. The antiviral activity of JFL in response to HSV-2 and CMV, either before or after viral infection of cell monolayers, was observed at different doses. This result differed markedly from the lack of effect reported for collecting, mannan binding protein, and bovine conglutinin on HSV-2. This result suggests that JFL may act either on the surface of the host cell or directly on the viral envelope, there by inhibiting viral infectivity [6][7].

8. ANTI-BACTERIAL ACTIVITY

Khan et al. studied the antibacterial effects of the crude methanolic extracts of bark, stem and root, heart wood of stem and roots, leaves, fruits and seeds as well as their petroleum, dichloromethane, ethyl acetate and butanol partitioned fractions on Bacillus cereus, B. coagulants, B. megaterium, B. subtilis, Lactobacillus casei, Micrococcus luteus, M. roseus, Staphylococcus albus, S. aureus, S. epidermidis, Streptococcus faecalis, St. pneumonia, Agrobacterium tumefaciens, Citro bacterfreundii, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumonia, Neisseria gonorrhea, Proteus mirabilis, P. vulgaris, Pseudomonas aeruginosa, Salmonella typhi, Salmonella typhymurium and Serratiamarcescens by the disc diffusion method at standard concentration of 4 mg/disc and chloramphenicol (10 µg disc) as positive control. It was observed that of all the extracts and fractions investigated the butanol fractions of the root bark and fruits were found to be the most active [2][3].

9.IMMUNOMODULATORY EFFECT

Jacalin, the major protein from the jackfruit (Artocarpus heterophyllus) seeds, is a tetrameric two-chain lectin (molecular mass 65 kDa) combining a heavy chain of 133 amino acid residues with a light β chain of 20–21 amino acid residues. It is highly specific for the O-glycoside of the disaccharide Thomsen–Friedenreich antigen (Galβ1–3GalNAc), even in its sialylated form. This property has made Jacalin suitable for studying various O-linked glycoproteins, particularly human IgA1[35]. Jacalin's uniqueness in being strongly mitogenic for human CD4+ T lymphocytes has made it a useful tool for the evaluation of the immune status of patients infected with human immunodeficiency virus (HIV)-1. The abundance of source material for the production of Jacalin, its ease of purification, yield and stability has made it an attractive cost effective lectin. It has found applications in diverse areas such as the isolation of human

plasma glycoproteins (IgA1, C1- inhibitor, hemopexin, 2-HSG), the investigation of IgA nephropathy, the analysis of O-linked glycoproteins and the detection of tumors' [11].

10. ANTI-MALARIAL ACTIVITIES

The flavonoids especially artonin, artocapones show anti-plasmodial activity. Antimalarial effect of some selected isolated flavone derivatives showed that artonin E exhibited very strong inhibition (IC50 0.1mg/mL) against Kl strain in comparison against 3D7 strain of Plasmodium falciparum (IC50 0.3 mg/mL) [74,60]. A related prenylated flavone, namely 12-hydroxyartonin E, exhibited strong inhibition (IC50 0.9 mg/mL) against Kl strain, but weak inhibition (IC50 14.3 mg/mL) against 3D7 strain. Those two compounds were the member of 3-prenylflavone type. In addition, the other isolated flavone derivatives showed moderate inhibition with IC50 respectively 2.1, 1.6, 3.6, 1.3, 6.7 and 2.1 mg/mL against both the strain of P. falciparum, except for flavanone-3-ol derivative (dihydromorin), which had no inhibition [12].

11. ANTIFUNGAL ACTIVITIES

The studies jackfruit Two novel chitin-binding lectins from seeds of Artocarpus genus were described, one from jackfruit and one from breadfruit. They were purified from saline crude extract of seeds using affinity chromatography on chitin column, size exclusion chromatography and reverse-phase chromate-graphy on the C-18 column. Both are 14 kDa proteins, made up of 3 chains linked by disulfide bonds. The partial amino acid sequences of the two lectins showed they are homologous to each other but not to other plant chitin-binding proteins. Thus, they cannot be classified in any known plant chitin binding protein family, particularly because of their inter-chain covalent bonds. Their circular dichroism spectra and deconvolution showed a secondary structure content of beta sheet and unordered elements. The lectins were thermally stable until 80 degrees C and structural changes were observed below pH 6. Both lectins inhibited the growth of Fusarium moniliforme and Saccharomyces cerevisiae, and presented hem agglutination activity against human and rabbit erythrocytes. These lectins were denoted jackin (from jackfruit) and frutackin (from breadfruit). it seeds shown to inhibit growth of Fusarium moniliform and Saccharomyces cerevisiae [22].

CONCLUSION

Cancer is becoming a high profile disease in developed and developing worlds. In 2017 the WHO Published that in 2015, 7.6 million people died from cancer related diseases with the majority of these people living in low-income countries.

Experimental studies performed in the past suggest that, jackfruit possesses diverse medicinal uses including antioxidant, anti-inflammatory, antimicrobial, anti-cariogenic, anti-neoplastic and hypoglycemic effects, inhibits melanin biosynthesis, possesses wound healing properties, and causes a transient decrease in the sexual performance. The plant kingdom such as polyphenols, flavonoids and brassino steroids have been studied for their potential use as anticancer agents.
Collectively they have been shown to possess anticancer activities which include; antioxidant activity; inhibition of cancer cell growth; induction of apoptosis; target specificity; cancer cell cytotoxicity.

Plant-derived drugs have been developed from positive results in research and have progressed into clinical trials. The observed pharmacological properties may be attributed to the presence of various phyto-chemicals and from the results obtained from MTT and SRB assay methods, by the comparison of the IC50 values and linearity of the activity, the methanolic extract of Artocarpus heterophyllus showed excellent cytotoxicity against the A549 cell line, but had not activity against MCF-7 cell lines.

Target specific agents that are capable of inducing selective apoptosis of cancer cells, but are harmless to normal cells are receiving considerable attention in the fields of cancer prevention and therapy. Therefore, Artocarpus heterophyllus is a candidate for development as a Chemo preventive agent.

There are only a few recent studies that have focused on the extending shelf life of jackfruit and value addition of jackfruit waste by converting them to different products and renewable energy sources. Thus, more researches should be devoted for discovering possible industrial applications of jackfruit and proper management of waste generated in jackfruit processing.

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To accomplish great things, we must not only act, but also dream; not only plan, but also believe. Believe in our self and may the impossible be the smaller word.

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