INTERNATIONAL NEUROUROLOGY JOURNAL

Phytochemical and Biological Investigations of Alphonseasclerocarpa Thaw. (Annonaceae family): Potential for Cancer Therapy

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Abstract
Phytochemicals are non-nutritive compounds found in plants that greatly influence its flavour and colour. These biologically active substances are known for their potential health advantages in the prevention of numerous diseases, including cancer. They are categorised into five primary groups: phenolics, carotenoids, organosulfur compounds, nitrogen-containing compounds, and alkaloids. The genus Alphonseasclerocarpa Thwaites (Annonaceae) includes species distributed widely in the tropical areas. Whole plant of A. sclerocarpa is traditionally believed for its eminent therapeutic benefits. Despite its medicinal properties the plant seems to be less explored and hence this research aims at exploring the Pharmacognostical parameters for standardization. The aim of this review article is to investigate the possible therapeutic effects of A. sclerocarpa dietary phytochemicals, including carotenoids, flavonoids, phenolic acids, phytosterols, and stilbenes (secondary metabolites), in the treatment and prevention of cancer, using data from clinical trials and epidemiological research. Most available clinical trials were unable to replicate the significant benefits of increased consumption of phytochemicals and elevated serum levels of these compounds, despite most epidemiological studies reporting a link between increased exposure and a lower cancer risk across most cancer types. Many these trials were terminated early for lack of data or safety concerns. Even with phytochemicals' potent anticancer effects and numerous epidemiological studies demonstrating their effectiveness, human studies and clinical trials are still desperately needed, with extra consideration applied to safety precautions. An overview of the epidemiological and clinical data pertaining to phytochemicals plants exhibit a potent anticancer activity for the development of drug discovery techniques.

Keywords: Pharmacognostical parameters, A. sclerocarpa, drug discovery, secondary metabolites, Cancer

Introduction
Non-nutritive compounds called phytochemicals are present in plants and greatly influence the taste, colour, and texture of both the plants and the drinks made from them. Their possible health benefits are also being investigated [1,2]. The role of phytochemicals as substrates for biochemical reactions, cofactors of enzymatic reactions, inhibitors of enzymatic reactions, absorbents/sequestrants that bind to and eliminate unwanted constituents in the gut, ligands that irritate or antagonise cell surface or intracellular receptors, scavengers of reactive or toxic chemicals, compounds that improve the stability and absorption of essential nutrients, selective growth factors for beneficial gastrointestinal bacteria, fermentation substrates for beneficial oral, gastric, or intestinal bacteria, and selective inhibitors of harmful intestinal bacteria are a few of the potential mechanisms underlying the health benefits of phytochemicals [3,4,5,6,7,8,9]. Numerous studies have demonstrated the potential of phytochemicals to prevent a wide range of illnesses, such as diabetes, osteoporosis, menopausal disorders, gastrointestinal issues, atopic eczema, hyperactivity, gynaecological, neurological, and immunological disorders, as well as cancer [10,11,12]. Based on available statistics, about 19.3 million new instances of cancer were diagnosed and recorded in the past year [13]. This is expected to result in over 10 million fatalities by the year 2020. Millions of people die from cancer every year because of its ongoing global increase in incidence, underscoring the urgent need for novel cancer control strategies. A different way to tackle this issue would be to concentrate on controlling carcinogenesis instead of trying to treat cancer as an advanced stage of the disease [14]. One approach to achieving this assumption is chemoprevention, which is the use of natural, synthetic, or biologic chemical compounds to reverse, suppress, or prevent carcinogenic progression to an invasive malignancy [15]. A suitable lifestyle change is thought to be able to prevent almost two thirds of human cancer cases, and diet has a significant role in 10–70% (or on average, 35%) of cancer deaths in humans. A growing body of research from both laboratory and population studies indicates that phytochemicals have strong antimutagenic and anticarcinogenic effects [16].

DOI: 10.5123/inj.2024.3.inj133
ISSN:2093-4777 | E-ISSN:2093-6931
Vol. 28 Iss. 3 (2024)

Phytochemicals are useful in the treatment and prevention of cancer, according to a few research conducted on animal models and cell lines, and the outcomes seem highly promising. Phytochemicals that are derived from medicinal plants have been shown to suppress angiogenesis, induce apoptosis, delay metastasis, and decrease cell proliferation. Humans have been blessed by nature with the presence of flora and fauna [17-18]. The various natural chemical components found in these plants and animals are responsible for their pharmacological and therapeutic efficacy. The Annonaceae family of plants is the least studied group of plants with significant medicinal potential, including antioxidant, anti-parasitic, and anti-cancer effects.

With over 123 genera and 2100 species, it is found across the tropical regions [19]. Annonaceae is thought to be the large-scale alkaloids production diligently (29% of total alkaloids), particularly the Benzylisoquinoline type. Annonaceae are thought to be the large-scale alkaloids producers (29% of total alkaloids produced), particularly those of the benzylisoquinoline type.

A. sclerocarpa thwaites, one of the Annonaceae members with the least amount of research on its pharmacological advantages, is chosen for this study. *A. sclerocarpa* is a low-lying tree that features simple, alternating leaves that vary in size from 2.5-6.5 × 2-3 cm, fissured bark, clustered flowers in cymes, and fruits that resemble aggregated berries that are part of the Annonaceae family. The plant is extensively found in tropical regions of the world, particularly in southern India and Sri Lanka. The plant is found in the South Sahyadri ranges and Western Ghats in South India [20]. It is commonly named as Pulusu Mamidi by the tribes [21]. Pharmacognosy deals basically with standardization as any of the products from herbal origin viz. Herbal Cosmetic or Herbal syrup made from pharmacologically important constituents can be introduced into the market only upon passing through all the Quality control parameters [22]. In other words, it is that only the standardized product is acceptable for human consumption. Continuous supply of standardized herbal medicines is only ensured when we have a proper control on starting material or Crude form of drug. In ensuring the quality of Herbal raw material as well the product Pharmacognostical, Physico-chemical and Phytochemical evaluations play a pivotal role.

According to Hadjzadeh*et al.'s*2005research, garlic inhibits the growth of the Hep-2 human laryngeal cancer cell line [23]. Research on the effects of Hibiscus sabdariffa leaf extract on human cell and xenograft models have shown that it causes human melanoma autophagic cell death, inhibits the growth of LNCaP in human cell models and xenograft tumour studies, and causes human leukaemia and gastric carcinoma cells to undergo apoptosis [24-27]. Shemamruthaa plays an important function in lowering LPO, avoiding membrane damage, and restoring membrane integrity, as demonstrated by the considerable anti-cancer effect it has been shown to have by Purushothaman *et al.,* 2013 in their work utilising a rat model [28]. In their investigation on a human cell line, Mortazavian *et al.,*2012 showed that the ethyl acetate and n-butanol fractions of Viola tricolour exhibit strong anticancer effects against the neuroblastoma N2a cells [29]. According to studies by Sadeghnia *et al.,* 2014 the ethyl acetate fraction of Viola tricolour has potential lethal characteristics by blocking angiogenesis on CAM, causing apoptosis, and lowering tumour cell growth. [30] In their study on the anticancer activities of several herbs and spices, Berrington *et al.,* 2012 found that species of rosemary had a high antioxidant content, which may confer chemopreventive effects [31]. In the study conducted by Chaudhry *et al*., [32], *Vitrexrotundifolia* fractions induced apoptosis in a human breast cancer cell line. The study by Jo KJ *et al.,*2012on the cytotoxic effects of *Vitexrotundifolia* on human colon cancer cell lines revealed that the herb suppressed the development of HT-29 cells [33]. Even yet, there aren't many available human investigations and clinical trials [34-37]. Phenolics, carotenoids, organosulfur compounds, nitrogen-containing compounds, and alkaloids are the five main classes of biologically active phytochemicals that can regulate carcinogenesis at different phases [38]. In this paper, we want to present a comprehensive review of the research on the impact of the specific compounds in oncology together with an overview of phytochemicals' involvement in cancer prevention especially in the medicinal plant *A. sclerocarpa.*

Development of Cancer and Phytochemical Pathways of Action

To determine the precise mechanism of carcinogenesis, numerous studies have been carried out over time. The multistep process of carcinogenesis, which is split into three primary phasesinitiation, promotion, and progressionwas shown by Sporn and Liby [39]. Most of the time, when a carcinogen enters the body, it is detoxified. On the other hand, several metabolic pathways may activate it. Carcinogenic substances raise oxidative stress, damage DNA, and trigger the start of carcinogenesis, claim Klaunig and Wang [40]. Carcinogenic substances, according to Klaunig and Wang [41], cause oxidative stress, damage DNA, and trigger the start of carcinogenesis. During the promotion phase, started cells begin to proliferate, which causes the preneoplastic cells to accumulate. During the third and final phase, also known as the progression phase, these preneoplastic cells start to invade and spread throughout the body. As the figure 1 illustrates, the progression phase cannot be reversed.

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ISSN:2093-4777 | E-ISSN:2093-6931
Vol. 28 Iss. 3 (2024)

INJ INTERNATIONAL NEUROUROLOGY JOURNAL

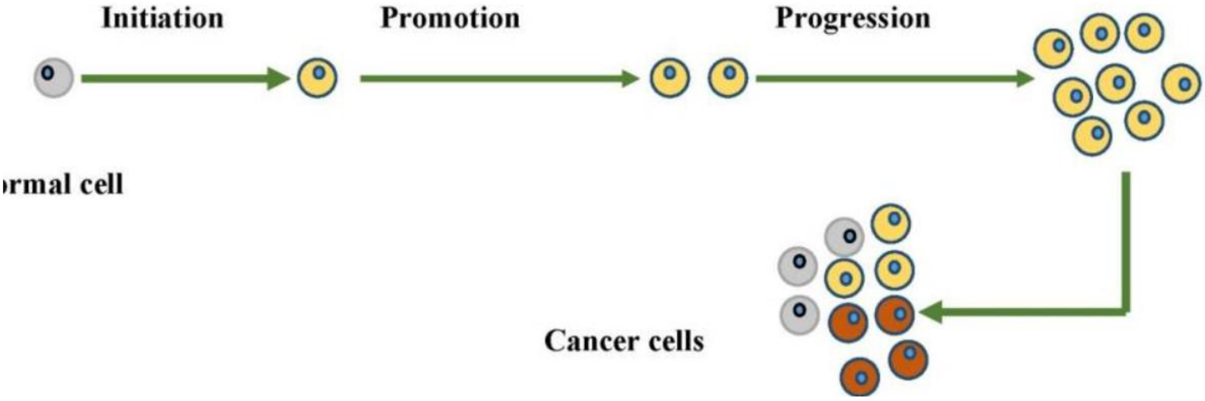

Fig 1: Diagrammatic representation of carcinogenesis process.

Steps Involved in the Development of Phytochemical Drugs from the Medicinal Plants especially in the *A. sclerocarpa*

A. sclerocarpa as medicinal agents is based on the calibre of their active phytochemicals. The age, season, and environment of the plants are other important elements that influence the quality of phytochemicals in plants. However, additional study is required to increase our understanding of phytochemicals and how they might be used to prevent and treat cancer. As shown in Figure 2, some plant portions have higher concentrations of bioactive phytochemicals than others. The active phytochemical can be purified using a variety of methods, such as combinatorial chemistry, isolation tests, and bioassay-guided fractionation [42].

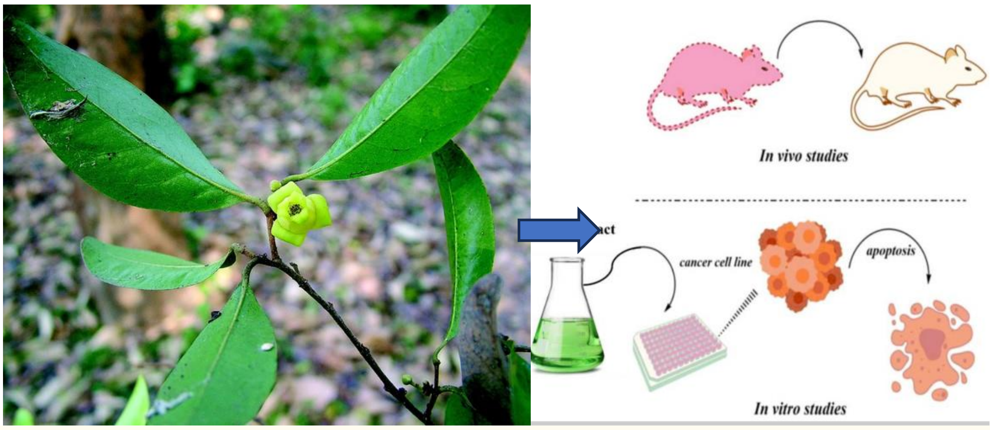

Fig 2: Assessment of phytochemicals from medicinal plant *A. sclerocarpa*for anti-cancer activity.

For bioassay-guided fractionation, a variety of analytical methods can be employed to extract bioactive molecules from a mixture of chemicals. Tests using natural extracts from either dry or wet plant material are the first step in assessing biological activity [42]. Appropriate matrices are used for the fractionation of the active extract, and different analytical techniquesmass spectroscopy, HPLC, TLC, FTIR, and NMRare employed to separate the active components. A wide range of solvents are available for use in the separation process. Superdex, silica, and other appropriate matrices can be utilised for the fractionation. Therapeutic plants include naturally occurring bioactive chemicals that can be found using a variety of colours. Additionally, these phytochemicals are examined for their anti-cancer properties in vivo or in vitro after their purification is finished. Future medication design is centred on factors including pharmacokinetics, metabolic fate, dose determination, immunogenicity, pharmacodynamics, and drug interaction when anti-cancerous outcomes are attained [43].

Major Phytochemical Constituents of the Annonaceae Family

One of the most diverse families within the magnoliid lineage, Annonaceae is a typical pantropical family of shrubs, trees, and lianas with roughly 112 genera and 2440 species [44]. The family has been assigned to Magnoliales, together with Degeneriaceae, Eupomatiaceae, Himantandraceae, Magnoliaceae, and Myristicaceae, based on molecular data [45]. Based on DNA sequences [46,47] and additional physical characteristics [48], the family is firmly believed to have monophyletic origins. It is widely regarded as a crucial element of lowland

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ISSN:2093-4777 | E-ISSN:2093-6931
Vol. 28 Iss. 3 (2024)

INTERNATIONAL NEUROUROLOGY JOURNAL

tropical rainforests worldwide [49-52], the diversity and quantity of which are influenced by temperature and precipitation [52].

Phytochemicals such as flavonoids, lectins, saponins, alkaloids, carotenoids, and phenolic acids are abundant in species belonging to the Annonaceae family (Figure 3). All Fabaceae genera include these phytochemicals, which have significant therapeutic potential [53, 54]. In terms of their ability to fight cancer, phytochemicals have garnered a lot of attention [42]. The Annonaceae family's phytochemicals, however, have not been thoroughly studied by numerous researchers worldwide. All these phytochemicals have strong anti-cancer properties against various human cancer types, based on the data that is currently available (Figure 5). Figure 4 displays the structures of many phytochemicals with anti-cancer properties that are present in various Fabaceae family members.

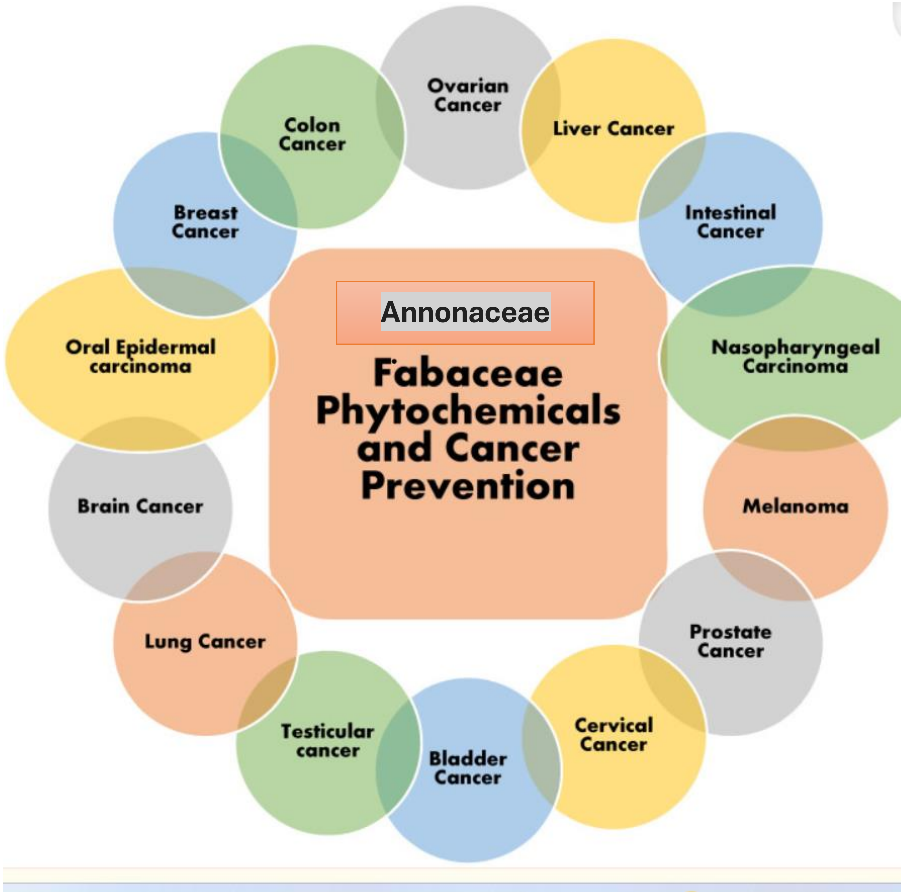
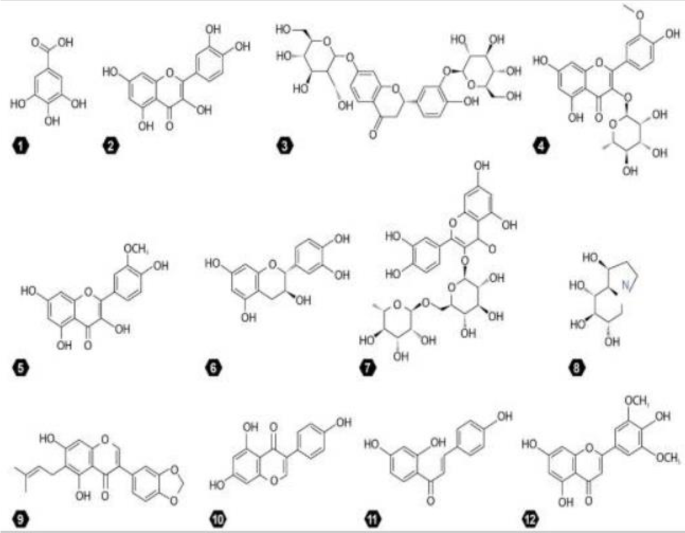


Fig 3: Reported activity of phytochemicals of family Annonaceae against various types of cancers.



DOI: 10.5123/inj.2024.3.inj133

ISSN:2093-4777 | E-ISSN:2093-6931

Vol. 28 Iss. 3 (2024)

INJ INTERNATIONAL NEUROUROLOGY JOURNAL

Fig 4: Structure of main phytochemicals from family Fabaceae. 1. Gallic acid. 2. Quercetin. 3. Butrin. 4. Isorhamnetin-3-O-rhamnoside. 5. Isorhamnetin. 6. Catechin. 7. Rutin. 8. Castanospermine. 9. Derrubone. 10. Genistein. 11. Isoliquiritigenin. 12. Tricin.

Alkaloids:

Alkaloids are essential secondary metabolites that are useful for the development of new medications. Alkaloids have been shown in numerous studies to possess anti-proliferative and anti-cancer qualities [55]. Vinblastine, vindesine, vinorelbine, and vincristine are the best-known alkaloids that have been effectively created as anti-cancer medications. Testicular, brain, lung, bladder, and melanoma cancers are among the cancer types that these are successful against. There are over 21,000 distinct alkaloids known to exist, and most of them are excellent sources of medication, particularly when it comes to their anti-cancer properties [56].

Flavonoids

Flavonoids are recognised for their anti-angiogenic properties and are regarded as potent antioxidants. Flavonoids have been shown in numerous studies to prevent the metabolic activation of carcinogens and to halt the formation of aberrant cells that could eventually turn into malignant cells [57]. Within the Fabaceae family, flavonoids and their derivatives are regarded as essential phytochemical components. Chalcone, flavones, flavonol, isoflavones, a flavonol glycoside, prenylated flavonoids, and lavandulyl flavanones are the most significant flavonoids that have been isolated from the different members of the family [58]. Prenylated flavonoids from some Fabaceae family members are known to have antioxidant and anti-cancer properties, according to Krishna *et al.* [59].

Phenolic Acids

Essential phytochemicals called phenolic acids are found in significant concentrations in Fabaceae family members. Non-flavonoid phenolic compounds, or phenolic acids, can exist in three different forms: free, conjugated soluble, and insoluble bound. However, a large range of plant species contain these non-flavonoid phenolic chemicals [60]. Ferulic acid, vanillic acid, caffeic acid, benzoic acid, p-hydroxy acid, 3,4-dihydroxybenzoic acid, sinapinic acid, and syringic acid are examples of natural phenolic acids found in different members of the Fabaceae family [61]. Recently, phenolic acids—secondary compounds—have been investigated for their potential to treat a variety of illnesses, most notably cancer.

Conclusion And Future Direction:

An abundance of phytochemicals, such as flavonoids, lectins, saponins, alkaloids, carotenoids, and phenolic acids, can be found in species belonging to the Annonaceae family. Because the phytochemicals found in Annonaceae members are useful in both the prevention and treatment of cancer, consuming a variety of Annonaceae species reduces the risk of developing cancer. While some of these phytochemicals have already been used in cancer treatments across the globe, other phytochemicals are also becoming more and more significant. These phytochemicals inhibit cancer by multiple methods, such as immune system modulation, apoptosis, antioxidant stress, induction of cell cycle arrest, and carcinogen inactivation. However, further investigation is warranted to evaluate the potential anti-carcinogenic effects of phytochemicals belonging to the Annonaceae family. Additional information about the anti-cancer potential of this family phytochemicals is required, and this information could result in the development of new pharmaceuticals derived from these phytochemicals. In a similar line, additional research is needed in the future to clarify the processes underlying phytochemicals' anti-cancer effects. Even if several phytochemicals in plants such as *A. sclerocarpa* are helpful, it's important to determine whether these phytochemicals have any synergistic effects on one another when it comes to fighting cancer in a single plant. Any long-term negative side effects on patients' physiological changes brought on by various anti-cancer phytochemicals from the Fabaceae family also need to be clarified. There are several publications regarding the effectiveness of various phytochemicals in combating cancer; however, the most of these reports are based on *in vitro* or *in vivo* experimentation, and there aren't many data on clinical trials. Further research will therefore require more clinical trial results attesting to the effectiveness of phytochemicals derived same family members with responsible mechanisms. Significant standardisation of potential phytochemicals in terms of methods for evaluating their safety, efficacy, composition, manufacturing processes, regulatory and approval criteria, and bioavailability is necessary to meet the international standard.

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ISSN:2093-4777 | E-ISSN:2093-6931
DOI: 10.5123/inj.2024.3.inj133
Vol. 28 Iss. 3 (2024)