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Therapeutic Potential of Plant Species Derived from Some Annonaceae Genus

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Abstract The Annonaceae family is rich in potential as a source of therapeutic agent for the development of novel pharmaceutical drugs. Several species belonging to Annonaceae genus have been well studied and have provided numerous therapeutic substances which able to use for the treatment of many illness. In this paper, four therapeutic potential of many species derived from some Annonaceae genus will be discussed based on previous published research for future testing usage.

Keywords Annonaceae, Antioxidant, Anticancer, Antimicrobial, Antiulcerogenic, Antimalarial

1. Introduction

The quantity of plant species in Malaysia is assess to be more than 23,500 species which incorporating 8,500 in Peninsular Malaysia and 15,000 in the East. However, just modest bunches of plants have been examined for their potential bioactivities and there are still numerous of them waiting to be discovered.

In plant taxonomy history, Annonaceae are a family name of flowering plant which comprises of 105 genera and 2500 species (wiki). Annonaceae plants mainly found in tropical area which generally distributed from Myanmar, through Indo-china, Malaysia and into north-eastern Queensland in Australia (thesis). In Malaysia, there are 38 genera, 198 local and 5 developed species including 17 varieties of Annonaceae plants and they are liberally found in the marsh woodlands usually beneath 2,000 feet [1].

Since the beginning of mankind, plants and herbs were used to treat various symptoms of diseases by the indigenous people and traditional healers [2]. Moreover, the herbal therapies have developed traditional medical systems such as Ayurveda and traditional Chinese Medicine Ancient Chinese, Indians, and North Africans provided written evidence of man's ingenuity in utilizing plants for the treatment of a wide variety of diseases as early as 3,000 BC [3]. When chemical analysis first became available, man began to perform plant extract by isolating the active compounds from medicinal plants using different types of solvents. Natural products possess of therapeutic agents has evolved to sophisticated isolation of active chemical constituent from ethnopharmacological plants [4].

However, there are some challenges in therapeutic of plant species. Approximately 25% of all plants that demonstrated promising biological activity in rapid assay fail to generate positive results confirmed on subsequent re-collections [5]. The issue probably due to plants inherent their chemistry variability, mislabelling and wrong taxonomic identification. Collecting plant samples seems easy, but actually it can be a challenge as it requires preliminary planning such as what is the standard procedure must be made to collect the plants (eg: permit) and does the plants are threatened or endangered [6].

The usage of chemical compound derived from plant species may cause some side effects due to immonotoxins [7, 8]. As example, Ricin is present in the seeds of castor bean or scientifically known as Ricinus communis. Ricin able to inactivate the ribosome and kill eukaryotic cells has been explored for therapeutic use in cancer treatment. The challenge of using ricin as therapeutic agent could be difficult because of the non-specificity of B chain, immunogenicity, and its low blood residence time [9-11]. In addition, the ricin immunotoxins also may present on the surface of normal cells leading to severe side effects. For example, therapeutic uses of ricin immunotoxin have been limited by the vascular leak syndrome (VLS), a side effect resulting from inappropriate toxin targeting to the capillary bed of endothelial cells, causing tissue edema and multi-organ failure [12].

Production of pharmaceutical proteins in plants are the fastest growing class of drugs for the treatment of various

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disease as it could produce the desired proteins by inserting a segment of DNA that encodes the protein of choice into plant cells and are only grown for the purpose of pharmaceutical applications. Despite of this benefit, there are numerous potential risks associated with plant-based pharmaceuticals which include contamination of non-transgenic crops intended for the consumption by humans, pollen transfer to related species, detection of non-target organisms which are not intended to be affected by the plant-produced protein [13]. Another significant side effect of using pharmaceutical protein in plant is allergic reactions to the drugs produced from the genetically engineered plants. All pharmaceutical product on the market can cause allergic reactions in some people. However, for those people who are not taking the drug could happen to inhale or dealing with pollen from the genetically engineered plant might getting allergic as well [14].

Traditionally, Annonaceae plants have been used for medicinal purposes such as stomachache, asthma, cough, fever and wounds [15, 16]. Annonaceae plant or locally known as Mempisang was listed as one of the local medicinal plants regularly used by the local healers to treat clinical symptoms [17]. In the present study, seven potential of pharmaceutical agent derived from Annonaceae species will be gathered and discussed.

2. Anti-Oxidant Potential

(Cherimoya)

Cherimoya is a common name of *Annona cherimola Mill* which means cold seeds [18]. Despite the fact that the plant does not tolerate freezing temperatures, it is still able to develop at high altitudes due to the germination of the seeds at higher elevations [19]. The species began in South America, yet is currently become all through Africa, India and different parts of Asia, Australia, and New Zealand.

Cherimoya fruits are eaten as daily consumption of vitamin C and it also contains approximately 15% of sugar around 60kcal/100g [20]. Previous test revealed that high consumption of Cherimoya fruits may cause atypical Parkinsonism in Guadeloupe [21, 22]. However, the bark extracts may potentially act as anaesthetic agent if infused.

Pulp of ripe fruit extracts of Annona cherimola Mill in methanol, ethanol and dimethyl formamide (DMF) have been demonstrated a decent radical scavenging activity towards DPPH radical. However, DMF extract obviously predominant then the other two extracts with high capacity of quenching DPPH radical reaching up to 69% of inhibition. Cherimoya pulps are compelling free radical scavengers because of the hydroxyl groups linked to phenolic structure present in the extracts [23].

(Pisang Tandok)

The common name of *Uvaria grandiflora Roxb* is *Pisang Tandok* and it is a fantastic climber from the south of Thailand. The plant is utilized locally as daily consumption since the fruits are aromatic and fleshy [24]. In addition, their leaves and roots are applied in traditional medicine against stomach-ache, abdominal pains and skin diseases [25-28]. In Sabah, Malaysia, the leaves has been used among Kadazan/Dusun communities to treat colds and shivers for children in grounded paste and used as poultice to wrap around the abdomen part [29].

Stem barks ethanolic extract of *U.grandiflora Roxb* in antioxidant test is higher than the leaves. The radical scavenging activity of the stem barks reached to 95.32% at IC_{50} value of 100 µg/ml being the most potent free radical inhibitors and act as primary antioxidants [30]. This result has confirmed earlier studies done on many Uvaria species [31, 32].

(Jari Jari)

A.dolichocarpa locally called as Jari jari or Yara yara [33] which originating from Guyana in South America. It is widely distributed and being the most common neotropical species of Annonaceae [34]. Traditionally in Thailand, Anaxagorea has been used as a blood tonic, stomachic and antipyretic [35]. Their leaves also usually used as tropical for articular rheumatism and could be applied for the treatment after childbirth [36].

The stem bark of *A.dolichocarpa* chloroform extract had relatively powerful DPPH radical scavenging activities (IC_{50} 55.64 ± 5.24 µg/ml) which complement their total phenolic content (252.50 ± 7.02 mg of gallic acid equivalent/g) thus, illustrating its high antioxidant capacity [37].

(Pindaíba-da-mata)

Duguetia genus commonly occurs in several regions of Brazil such as Bahia, Espírito Santo and Minas Gerais. It is known as Pindaíba-da-mata in Brazil [38]. Various parts of Duguetia have been utilized in folk medicine. As example, its leaves and twigs were used to treat rheumatism and renal colic meanwhile the seed was used against pediculosis by blended into powder and mixed with water [39].

For *D. chrysocarpa*, the stem bark ethyl acetate extract demonstrated the most critical total phenolic content (213.11 ± 9.87) which contributed to the lowest IC_{50} value (26.97 ± 1.90 µg/ml). This finding supports that the presence of phenolic compounds influence the antioxidant activity in plant which convey scavenger properties [37].

3. Anti-microbial Potential

(Custard apple)

Past experiment documented that most of Annonaceae plant with outstanding anti-microbial activity derived from Annona family which locally known as custard apple. There were 4 major species has been identified as a potential anti-microbial agent which are *Annona salzmanii, A. pickeii, A. cherimola and A. foetidaced.* The essential oil from the leaves of A. salzmanii and A. pickeii managed to detect 61 chemical constituents analyzed by GCMS. All compounds in both species has illustrated significant minimal inhibitory

concentration (MIC) within the range of 25-100 μg/mL^{-1}. [40]

Whereas for A. cherimola, monoterpenes and sesquiterspenes were the major compound detected in three essential oil extracted form their leaves, flowers and fruits. High level of sesquiterspenes in essential oil from the leaves and high level of monoterpenes in essential oil from the flowers showing poor anti-microbial activity against assayed microorganism with minor MIC values due to the decomposition of either hydrocarbon, alcohol or oxides in both part of the plant. [41, 42]

The essential oil extracted from A.foetida leaves showing strong activity against five out of eleven tested microorganisms. The growth of Candida albicans and Rhodococcus equi were significantly inhibited by this species at MIC value of 60 μg/mL^{-1}. [43]

(Negro Pepper)

The fruits of Xylopia have both nutritional and medicinal uses. In cooking, the fruits are use as spice in various traditional dishes of Western and Central Africa therefore it commonly named as Negro pepper [44]. Medically, the fruits are useful in the treatment bronchitis and dysenteric conditions, and as a medicine for bulimia [45]. This plant is native to the lowland forest in the savannah zones of Africa however largely found in West, Central and Southern Africa largely located in West, Central and Southern Africa. These trees are generally circulated in the moist forest zones of West Africa especially along rivers [46].

An impressive finding of fruit essential oil of X. aethiopica demonstrated high level of oil constituent (18.3%) therefore leading to its active anti-microbial activity by showing MIC value within a range of 18-32 μg/mL against 8 tested microorganisms which including *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus faecalis, Corynebacterium glutamicum, Bacillus cereus, Bacillus subtilis, Aspergillus flavus.* [47]

In the comparison of ethanolic extracts and aqueous fraction from the leaves of Xylopia aethiopica, aqueous fraction illustrated better potential as it produced lower MIC value (15 μg/mL) against three out of five tested pathogenic organisms (E. coli, P. aeruginosa and S. fecalis.). However, ethanolic extracts of this species still managed to inhibit all of tested microorganisms but only with higher MIC value (30 μg/mL) [48].

Despite of anti-microbial activity in aqueous fraction, other study reported that ethanolic extract of X. aethiopica, leaves and seed showing greater inhibiting effect against S.aureus, P. aeruginosa, E.coli compare to water extract in the used of paper disc and agar gel diffusion method by which ethanol extracts produced wider inhibition zone range from 3-22mm against tested microorganisms. This finding, supported that those bioactive ingredient composed in this psecies was better extracted with ethanol than water. [49]

(Ashoka Tree)

P. longifolia is native to India and Sri Lanka. This plant locally named as Ashoka tree in India [50]. It is a tropical, lofty and evergreen tree. Usually, Ashoka tree usually found in dry and lowland forest. Ashoka tree has Javaranashaka (reducing fever) action especially in their bark [51]. Therefore, traditionally it has been used in the treatment of fever and others clinical symptoms such as skin diseases, diabetes, hypertension and helminthiasis [52].

Several parts of this species has been investigated for their antibacterial and anti-fungal potential as it composed multiple chemical constituent such alkaloids which contribute this potential. Two isolated compound which is diterpenoids 16α-hydroxy-cleroda-3,13 (14)-Z-diene-15,16 -olide (1) and 16-oxo-cleroda-3, 13(14)-E-diene-15-oic acid (2) have been extracted from the seed of P. longifolia using hexane. According to the study, both compound provided active anti-microbial activity as compound 1 showing more active against gram (-) bacteria such *as E. coli, K. aerogenes, Pseudomones species and S. lutea* while compound 2 against all the bacteria tested *(Arthrobacter citreus, Bacillus cereus, B. licheniformis, B. polymyxa, B. pumilus, B. subtilis, Clostridium sp., Staphylococus aureus, Streptococcus sp., Escherichia coli, Klebsiella aerogenes, Pseudomonas aeruginosa, P. putida, Salmonella typhimurium, Sarcina lutea and Nocardia sp.* [53].

Other study on the root of this species has isolated 3 new alkaloids namely as pendulamine A (1), pendulamine B (2) and penduline (3). The pure compounds showing significant antibacterial activity as the MIC value proven that compound 1 and compound 2 have promising anti-microbial activity against *C. hoffmanii, M. lysodicklycus, S. typhi, S. aureus, S. paratyphi A, B. subtilis, K. pneumoniae, P. aeruginosa, S. viridans, S. pyogenes, C. hoffmanii, S. viridans M. lysodicklycus, S. aureus, S. paratyphi A, S. typhi, S. faecalis, K. pneumoniae, and S. pyogenes*. while compound 3 displayed poor potential [54].

Phytochemical screening on the leaf of P. longifolia has detected seven major compound, which are steroids, alkaloids, biterpenoids, amino acids, essential oil, phenolics and flavonoids. These compounds were claims to be responsible for its anti-microbial potential as the leaf extracted with methanol and hot aqueous exhibited great anti-microbial activity especially against K. pneumoniae, E. coli and B. subtilis. Additionally, antibiotic sensitivity test also has been conducted against all of the reference bacteria (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris and Enterobacter aerogenes*) to determine their antibiotic sensitivity profile towards Amoxycillin (30μg), Gentamycin (10μg), Cloxacillin (10μg), Ofloxacin (5μg), Kanamycin (30μg), Tetracyclin (30μg), Ciprofloxacin (5μg), Penicillin G (10μg), Norfloxacin (10μg), Ampicillin (10μg), Tobramycin (10μg) and Cephalexin (10μg). As a result, all reference bacteria was resistant to all of tested antibiotic therefore cannot be used as a treatment therapeutic for diseases related with reference bacteria [55].

4. Anti-cancer Potential

(Mempisang)

The genus can be found at Peninsular Thailand and Peninsular Malaysia. Currently, about 52 Pseuduvaria species were classified and documented. Pseuduvaria locally known as "Mempisang", which can be found in the forest in Perak, Pahang, Terengganu including the Tioman Island, Malaysia [56].

For the past of 5 years, there was a number of research has been done to investigate the cytotoxicity potential of few Pseuduvaria species including *P. monticola, P. macrophylla and P. rugosa.* Literature survey claims that these species does shows promising cytotoxic effect towards several human cancer cell lines determined by MTT assay as a method. The composition of various bioactive compound leading to their anti-cancer potential demonstrated by spectrophotometry analysis.

Phtochemical screening on P.rugosa stem bark has detected 2 known compound (Ouregidione and N-methylouregidione) and 3 unknown compound namely as Pseuduvaria A, Pseuduvaria B and Pseuduvaria C. Ouregidione, N-methylouregidione and pseuduvarine C displayed moderate cytotoxic activity on seven types of cancer cell lines (Breast MCF 7, Breast MDA-MB-231, Colon (HT-29, Lung A549, Pancreas PxPC-3, Prostate DU145 and Liver HepG-2). Whereas, Pseuduvarine A and Pseuduvarine B showed significant cytotoxicity against tested human cancer cell lines. [57]

A finding of a new benzopyran derivative known as isopolycerasoidol methyl ester was isolated from methanol extract of Pseuduvaria monticola leaves. Highly inhibition of cancer cells effect was observed in human breast cancer cells (MCF 7) under 48 hours treatment with IC50 value at 43µM. This study has proven that higher ROS production possess in this species has triggered the compound to induce apoptosis in MCF-7 cells thus leading to the elevation in membrane permeability [58].

Recent study on methanolic and hexanolic extract of P.macrophylla leave and stem bark has provided additional finding on the previous study as leaf methanolic extract strongly inhibited the proliferation of the breast cancer (MCF-7) with more than 80% of cell death compare to other cell lines. Meanwhile, leaf hexane extract showed inhibition of the proliferation mostly in breast cancer cell followed by colon cancer cells and prostate cancer cells under 24 hours treatment at 20 µg/mL [59].

(Chagau)

Historically, genus Miliusa comprised of 50 species which usually found in Thailand occurring from the Indian through Indo-china, Peninsular Malaysia, the southeast Asian islands to New Guinea and northern Australia [60]. The common name of this genus is *Chagau* [61]. Recently, few new species belongs to this genus has been describe namely as M. fragrans, M. hirsuta, M. intermedia, M. nakhonsiana, M. sessilis, M. thailandica, M. umpangensis and M. smithiae) [62]. Previous reports has documented several chemical constituents of plants in this genus such as isolation of 3,4-dimethoxy-6-styryl-pyran-2-one and (2E,5E)-2-methoxy -4-oxo-6-phenyl-hexa-2,5-dienoic acid methyl ester (styryl derivatives) from leaves and branches of Miliusa balansae [63]. In addition to that, the detection of a new flavone named 8-C-(o)-hydroxybenzylpachypodol] from Miliusa balansae has showed promising cytotoxic effect against three human cell lines (KB, Hep-G2, RD) with IC50 values < 5 µg/ml [64]. This finding really support that the member of Miliusa genus might possess bioactive compound which responsible to their therapeutic potential. Another cytotoxic study on the ethyl acetate extract of M. smithiae leaves and twigs also has reported potential anti-cancer activity due to the composition of 2 bioactive compound known as 5-hydroxy-3,7,4'-trimetoxyflavone (1) and 5,3'-dihydroxy-3,7,4'-trimetoxyflavone (2) [65].

5. Anti-ulcerogenic Potential

(Disepalum)

Enicosanthellum pulchrum is a tropical plant from Malaysia and this name synonym to Disepalum pulchrum (King) J.Sinclair [66]. This genus comprised of only two known species, which are Enicosanthellum petelotii and Enicosanthellum plagioneurum. [67]

Traditonally, indigenous people in Malaysia have been using this plant for the treatment of several disorders such as rheumatism, cough, fever, diarrhea, malaria, asthma, edema as well as gastrointestinal disorder. [68-70].

Despite of its traditional medicine potential, not much study has been investigated on the member of this genus even though recent study has reported their notable ulcer genic protection. Therefore, in the present paper, a review of this genus should be included to expose them for further investigation.

The leaves and stems ethanolic extracts of E. pulchrum at doses of 150 and 300 mg/kg have been given to a group of healthy adult male Sprague Dawley rats (6–8 weeks age and 200–220 g weight) after an acute toxicity study has confirmed both doses were safe to the animals as it showed no sign of toxicity. According to the microscopic evaluation and histology of gastric lesion) rats pretreated with 150 and 300 mg/kg of leaf and stem extract show mild lesions in the gastric mucosa and moderate mucosal disruption with edema and leucocyte infiltration in the submucosal layer. This therapeutic potential strongly supported by the composition of bioactive compound such as alkaloids, acerogenins, steroids or terpenoids detected in both extracts through observation of the HPLC chromatography. [71]

(Kiawi)

The common name of Mitrella Kentii is kiawi in Indonesian. While its synonyms are Melodorum pisocarpum and Me. Elegans [72].

There are 8 species that belogs to Mitrella genus which

including Mitrella aberrans, Mitrella beccarii, Mitrella dielsii, Mitrella kentia, Mitrella ledermannii, Mitrella mesnyi, Mitrella schlechteri and Mitrella sylvatica [73]. Mitrella kentia distributed from Antarctica, Brunei, Darussalam, India, Indonesia, Malaysia, Papua New Guinea, Singapore, Vietmam [74]. In Malaysia, it can be found at Peninsular Malaysia especially at Malacca Global plants [75] and traditionally used as a drink in the form of a root decoction to treat fever [76].

A single study on the Gastroprotective effect of desmosdumotin C compound isolated from Mitrella kentii hexane extract of the bark against ethanol-induced gastric mucosal hemorrhage in rats displayed decreased gastric ulcer area due to low or absence of edema, leucocytes infiltration and flattening of mucosal fold compared to the ulcer control group (5% Tween 80 v/v with absolute ethanol) after a group of rat pre-treated with 5 mg/kg, 10 mg/kg and 20 mg/kg of DES in vehicle with absolute ethanol. Additionally, decrease gastric ulcer area was demonstrated by the reduction of ulcer area formation of all DES doses within the range of 69.77%-90.18%. The first time discovery of this bioactive compound possess in this species has proven significant protection against gastric ulcer and potentially could be an anti-ulcerogenic agent in human as well [77].

(African Yellow Wood)

African yellow wood is a comman name of Enantia Chlorantha [78], which distributed from Africa, Central America, India and Malaysia [79]. Major characteristics that define this species is by having dense foliage leaves and spreading crown [80] of leaves that grows from 12-30 meter tall [81]. Due to its characteristic, it always found at high rainforest area.

Similar to Eniscosanthellum and Mitrella genus, not much species derived from this genus have been study in details for their anti-ulcerogenic potential. So far, only two study have been conducted previously which related to this species. However, a review on both study should be made in this paper, so that more biological and chemical study can be conducted. Traditionally, local people using its powdered bark and applied externally to treat sores, ulcer and wounds. (The Useful Plants of West Tropical Africa). In order to prove its potential scientifically, a study using bark of Enantia Chlorantha was done by isolating a new type of protoberberine alkaloid known as 7,8-dihydro-8-hydroxypalmatine. This compound was used as a sample for further investigation on its healing properties in rat by which the lesions have been caused by acetic acid, HCl/ethanol or absolute ethanol. Based on the result, this compound managed to increase gastric mucus production and accelerated ulcer healing [82, 83].

6. Conclusions

In summary, previous laboratory experiments and data have demonstrated that some Annonaceae species have significant therapeutic potential due to high decomposition of active compound that illustrated a strong correlation with their many biological activities against variety of diseases. Therefore, traditionally claimed of Annonaceae members of curing various health problems are justified. Moreover, the high bioactive properties of some Annonaceae species lead us to their application in pharmaceautical industry and as a natural therapeutic source. Assessing the therapeutic potentials of plants could insight us on how best these plants can be used in the treatment of diseases. An important aspect of the research that necessarily need to concern on is by focusing on laboratory work that involves definite method which could identify the patterns of used natural product and potential complication or side effects in order to improve conciliation effort of existing medication and to develop standard guideline for the usage of natural product on patient with various chronic diseases.

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