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Triterpenoids Isolated from *Cassia fistula* can be a Potent Anti-Tumor Agent: A Review

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Abstract: Cancer is a complex disease, among which the type of cancer affecting the female population is the breast cancer with high incidence and mortality rate. Since, the incidence and mortality rate are directly proportional to the population, the future perspectives of the breast cancer screening and treatments should be leveled up. Based on the hormone levels involved in the pathological causes of breast cancer it can be divided into various types i.e., Human Epidermal Growth Factor 2 (HER2), Oestrogen Receptor (ER) and Progesterone Receptor (PR) negativity. The metastatic property of breast cancer (the transferring of cancer to distant and different organs) is the primary reason for the incurability of the disease. This can be prevented by detection of cancer at a "possible early stage" and can be a better option at survival. Tumor markers play a vital role in identification or diagnosis monitoring and treatment.The number of cancer incidence and mortality rates are still through the roof inspite of innovative approaches available to take precautionary measures against breast cancer. Triterpenoids are the largest subfamily, classified based on their pentyl count, among the structurally diverse family of secondary metabolites Isoprenoids. Pentacyclic triterpenoids occur as free acids, esters or glycoside (saponins) and are the major class of the chemical compounds obtained from natural plant materials. Marine sponges, vegetables, fruits, cereals and spices are some of the common sources of triterpenoids. *Cassia fistula* belonging to the fabaceae family, has been used in the folklore medicine in different parts of South Asian countries and are native to Mexico, South Africa, India and Brazil. *C. fistula* is known for its wide range of pharmacological properties and in the practices of Unani and Ayurveda it is known as Argawadha also meant as "disease killer".

Keywords: Breast Cancer, Triterpenoids, *Cassia fistula*, Tumor Markers

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Introduction

Cancer is a disease that is complex, multifactorial and has high mortality rate globally (Kayan and Cinar, 2018). Among the different cancers affecting the female population, breast cancer has the highest incidence and mortality rate (Chen *et al.*, 2019). The number of breast cancer incidence is 100 times more in women than in men (Siegel *et al.*, 2017). It is reported as the second leading cause of death in both developing and developed countries for over 50 years now (Nigjeh *et al.*, 2018). In 2004, according to global cancer burden the death rate was 8.8 million and the estimation can increase with increase to population. The death rate is expected to increase by 10 folds in the year 2030 and the incidence may increase to 26.4 million (Donepudi *et al.*, 2014). The metastatic property of breast cancer (the transferring of cancer to distant and different organs) is the primary reason for the incurability of the disease. This can be prevented by detection of cancer at a "possible early stage" and can be a better option at survival (Wang *et al.*, 2016). In North America the patients with early/ timely detection of cancer had a better survival rate of relatively 5 years was more than 80% (DeSantis *et al.*, 2015). Sometimes breast cancer presents itself in the form of breast asymmetry, nipple discharge, palpable axillary mass, breast skin erythema, and breast skin thickening (Waks and Winer, 2019).

Breast cancer is classified under as luminal-A, luminal-B, Basal-like, normal- like and HER-2 enriched based on their gene expression and is termed under heterogeneous group of diseases (Perou *et al.*, 2000). Factors like incidence age, diagnosis, prognosis and response to treatment is where these intrinsic groups of breast cancer differ (Sotiriou *et al.*, 2003). Among these intrinsic groups a new type was identified in human and mouse breast tumors known as Claudin-low which has poor prognosis, Estrogen Receptor negative (ER-), Progesterone Receptor negative (PR-) and Human Epidermal Growth Facotr 2 negative (HER2-) these are also enriched with mammary stem cells, core EMT signature and Cancer Stem Cells (CSC) (Lim *et al.*, 2009). There are three major subtypes of breast cancer; Hormone Receptor Positive/Epidermal Growth Factor Receptor negative (HR+/ ERBB2-), Epidermal Growth Factor Receptor positive (ERBB2+) and Triple Negative (Waks and Winer, 2019). Among which the ERRB2+ type is the aggressive phenotype and has less response towards standard therapies and drugs (Caffarel *et al.*, 2010). In majority of the cancer cases, about 25% of the cases ERBB2 oncogene is overexpressed and are primarily responsible for tumor cell growth. ERBB2 addiction is the fundamental reason behind the behavior of such cancer cells (Stuchlmiller *et al.*, 2015). The Dimerization partner of ERBB2 is ERBB3/ HER3, Post translational and transcriptional Upregulation of ERBB3 is the reason behind any resistance created in the breast cancer cells towards therapy. Other Kinases like IGF1R, FGFR2, FAK, SRC family contribute towards resistance to therapies (Azuma *et al.*, 2011).

Out of all the breast cancer cases 15-20% of them are Triple negative breast cancer (TNBC) (Chengzhu *et al.*, 2019). The human epidermal growth factor receptor-2 (HER-2) and the progesterone receptor (PR) are absent in TNBC. It is vulnerable for the recurrence and metastatic property, and has an early onset of breast cancer. Recurrence after 1 and 3 years of diagnosis and majority of the deaths after 5 years of therapy are some of the salient features of TNBC. There are no drugs or treatment guidelines to be followed while treating TNBC (Dent *et al.*, 2007). TNBC is diagnosed for patients under 40 of age and are specific to certain race like, African American, the progression rate and overall survival is relatively low in TNBC patients (Hyslop *et al.*, 2013). On the basis of clinical, histological, and molecular profiling studies, TNBC can be divided into distinct groups ((Morris and Mitchell, 2008).

Screening:

Due to the sensitivity of the screening method's ability to identify breast cancer early, mammography or mammograms have been the

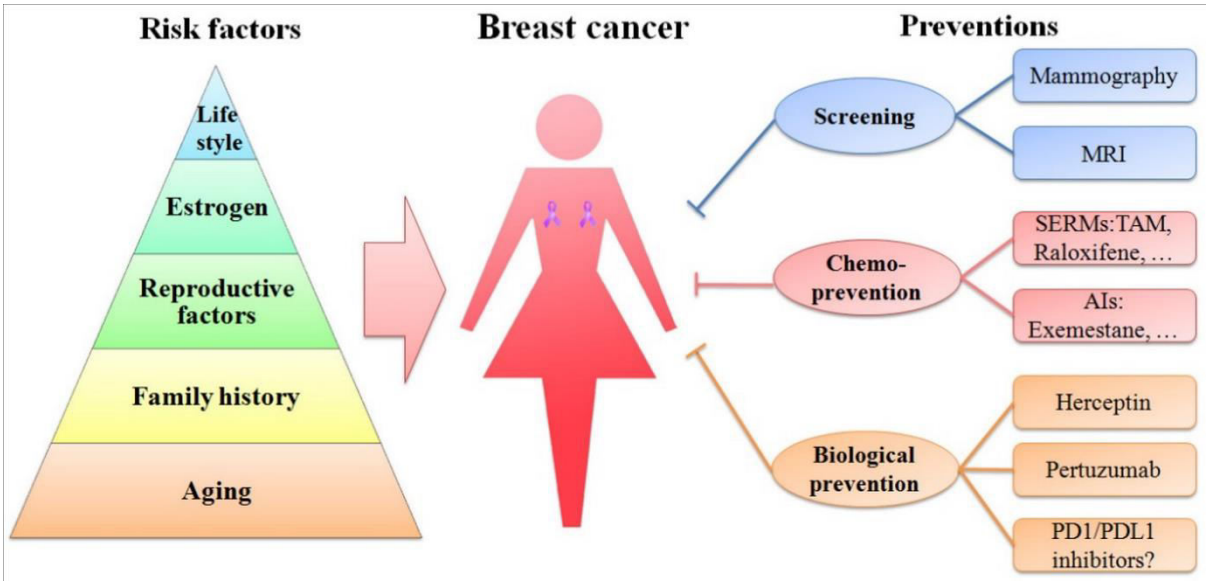

Fig.1: Risk factors associated with breast cancer.

main screening method for the identification of breast cancer over the past ten years. Magnetic Resonance Imaging (MRI) is another screening method which is much sensitive than the mammography in early detection of cancer (Drukteinis *et al.*, 2013).

Causes:

Age, sex, oestrogen hormone, gene mutation, family history, and unhealthy lifestyle are risk factors linked to breast cancer (Majeed *et al.*, 2013). The free radicals are a result of the metabolic changes due to the unhealthy food habits, and sedentary life style which in turn leads to increased cases of cancer (Fig. 1). The toxic free radicals are capable of creating chaos by stimulation cancer through damaging normal homeostasis of cells and oncogenic activation (Halliwell *et al.*, 2006).

There are many exogenous and endogenous factors that play a vital role in promoting the development of breast cancer and have different outcomes in each case (Elkaeed *et al.*, 2021). The induction of breast cancer is mainly due to genetic susceptibility and risk factors associated with it (Manikandan and Ramyachitra, 2017). The risk factors associated with breast cancer are yet to be found (Momenimohaved and Salenhiniya, 2019). Epithelial-mesenchymal transition (EMT) and cancer cell proliferation are contributing factors to the cancer's recurrence (Du *et al.*, 2019). Metastatic property of cancer serves as a major reason for the increased death rate due to breast cancer (Scully *et al.*, 2012).

Pathology:

The breast cancer incidence initiates with the dectal hyperproloferation which begins with benign tumor and by the constant trigerring action of various carcinogenic factors, eventually may lead to metastatic stage. The inititation and progession of breast cancer is due to the influence of stromal influence and macrophages in the cancer niche (Maffini *et al.*, 2004). Macrophages

are crucial in helping these cancer cells avoid immunological rejection and angiogenic angiogenesis by creating mutagenic inflammatory niches (Qian and Pollard, 2010). A new sub-class of malignant cells that are associated with initiation, recurrance and escape is cancer stem cells. These cells are capable of self-renewal and are resitant to therapies like chemotherapy and radiotherapy (Wang *et al.*, 2016).

Biomarkers:

Tumor markers play a vital role in identification or diagnosis monitoring and treatment.The disease outcome is not determined by the extended involvement of axiliary node. Tumour size and tumour grade are two important biomarkers widely used in the detection of metastatis(Bell *et al.*, 2017). In order to reveal the somatic mutation patterns, 104 TNBC samples were subjected to exome-sequencing, RNA sequencing, High Resoultion SNP ARRAYS and targeted Deep resequencing (Shah *et al.*, 2012). These arise revealed the most frequent aberration copy numbers, in which other genes like PARK 2 (Parkinson's disease 2), RBIP10 (Retinoblastoma gene 1), EGFR (Epidermal Growth Factor), PIK3CA, USH2A (Usher syndrome 2A) , MYO3A (myosin IIIA), were found frequently rather than the TP53 which was observed in 53% of breast cancers cases (Sporikova *et al.*, 2018). The profiling studies of gene expression plays a vital role in identification of "Gene signatures", that can be used to classify prognosis rate based on their phenotypes (Alizadeh *et al.*, 2000). Genes like IL3RA2, VCAM1 and MMP2 are aggressive breast cancer mediators, mediating towards lungs (Minn *et al.*, 2005), ST6GLANAC5 mediates metastatis towards brain (Bos *et al.*, 2009) and Cytokertain-19- Putative Marker of stem cells found in breast tissue (Gudjonsson *et al.*, 2002). Nm23, KAI1, BRAMS1 are some of the tumour suppressors that prevent detachment of cells from primary tumour. KISS 1, MKK4- reduced growth at the secondary tumour sites (Stark *et al.*, 2005).

The subset of proteins known as metastasis-including proteins (MIPs), which includes secreted phosphoprotein 1(SPP1), S100 Calcium binding proteins A4 (S100 A4), and S100P and anterior gradient 2 (AGR 2), were overexpressed in patients with sporadic and metastatic breast cancer (Bell *et al.*, 2017). The upregulation and downregulation of these gene signatures can be used to measure the prognosis rate. The main goals of breast cancer research in the future are to understand the metastasis processes, which include tumour cell intravasation, cells survival during circulation, extravasation into other tissues, and successfully inhibiting growth in secondary sites (Chambers *et al.*, 2002).

MMP1, VCAM1, FZD3, VEGFC, FOXM1 and MUC1 are breast cancer on set markers and are expressed in breast cancer neoplasms. With the help of IL4, MUC1 and VEGFC, TNF upregulates top breast cancer metastatic markers (Chizzolini *et al.*, 2000). RRM2 which inhibits WNT pathway when regulated by TNF (also associated in the pathways of P53) in signalling metastatis. In MBC diagonosis carcinogenic antigen (CEA) and cancer antigen 15-3 (CA 15-3) plays a vital role and the level of these antigens in the serum was observed along with Cancer Antigen 19-9 (CA 19-9), Cancer Antigen 125 (CA125) and Tissue polypeptide- specific antigen (TPS). When single tumor markers were used for the detection of breast cancer, the sensitivity was higher when compared to specificity rather than in analysis of combined tumor markers, where the specificity was higher.Whereas, CEA and TPS combined sensitivity was 78.7% and the specificity for the combination of CA15-3 and CA125 was 91.5%. Youden's index of CEA and TPS combined was 607% (Wang *et al.*, 2017) (Table 1).

Genes associated with breast cancer:

BRCA1/2:

The two famous oncogenes resposible for breast cancer risk are Breast Cancer Associated Gene – 1 and 2 (BRCA-1 and BRCA-2). Tumor supreesing proteins are encoded by both of these genes. disregualtion of cell cycle, duplication of abnormal centrosome is caused due to the deficiency in the

Table 1: Summary of sensitivity and specificity of individual markers

Individual markers	sensitivity	specificity
carcinogenic antigen (CEA)	56.7%	93.0%
cancer antigen 15-3 (CA 15-3)	44.5%	84.5%

Table 2: Location and functions of specific genes associated with breast cancer

Gene	Location	Function	References
BRCA-1	17q21	Tumor supressing gene	Deng *et al.* (2006)
BRCA-2	13q21	Tumor supressing gene	Sanchez *et al.* (2017)
EGFR	7p12	Proto-oncogene	Appert- Collin *et al.* (2015)
c-Myc	8q24	Proto-oncogene	Green *et al.* (2016)
p53	17p13.1	Tumor supressing gene	Varna (2011)
PIK3CA	3q26.3	Oncogene	Lifebvre (2016)
CCD1 (cyclin D1)	11q13	Oncogene	Inoue and Fry (2015)

expression of BRCA-1, genetic instability which eventually leads to apoptosis (Deng *et al.*, 2006). Whereas, BRCA-2 regulates the recombinational repair occuring in the double-stranded breaks of the DNA by interacting with RAD51 recombinase nad its important paralog DMC1 (Sanchez *et al.*, 2017). Eventhough the other allele is completely normal, the inheritance of BRCA-1/2 is autosomal domination. Out of all the breast cancer incidence due to heridity, 20-25% and 5-10% of all the breast cnacer cases are due to the BRCA-1/2 mutation (Balmana *et al.*, 2011).

EGFR:

In humans, the Epidermal Growth Factor Receptor (EGFR) can also be termed as c-ErbB-1 or Her-1. It is a cell surface glycoprotein belonging to the tyrosine kinase family. Promotion of cell proliferation, cell invasio, angiogenesis and escape from apoptosis is observed during the downsregulation of EGFR signaling (Appert-Collin *et al.*, 2015). In the Inflammatory Breast Cancer (IBC) which is an agressive sub-type of breast cancer, 30% are due to EGFR overexpression. It leads to poor prognosis in EFGR positive IBC patients (Alanazi and Khan, 2016).

TP53:

In all human malignancies and all subtypes of breast cancer, the aberrant expression of the TP53 gene (responsible for preserving homeostasis and genetic integrity) results in cell cycle arrest, DNA repair, and apoptosis (Hussain and Harris, 2006). The Node- negative breast cancer expression of Mutant TP53 leads to High proliferation, early disease recurrence, and early death (Allred *et al.*, 1993). For The unfavourable breast cancer outcomes, the mutated TP53 gene in the DNA binding domain (where it is frequently mutated) and substitution of missense codons are the major culprits (Sporikova *et al.*, 2018).

List of genes and their specific locations are mentioned in Table 2.

Therapeutic Approaches:

The number of cancer incidence and mortality rates are still through the roof inspite of

innovative approaches available to take precautionary measures against breast cancer (Heydarian *et al.*, 2020). In order to stop breast cancer from returning, the main goal of treatment for the disease is to remove tumors from the breast and lymph nodes nearby (Waks and Winer 2019). The current approaches towards breast cancer are surgical which poses risk due to the infections and complications that arise due to seroma and other side effects (Bodai and Tuso, 2019). Chemotherapy has been reported and known to have long-term and acute side effects on the patients affecting their quality of life. The women who can be cured by local treatment like radiotherapy and surgery are subjected to chemotherapy which can be considered as 'over-treated' and are needlessly exposed to the toxic effects of chemotherapy (Eifel *et al.*, 2000). Though there are different modes of treatment for breast cancer patients, tumor recurrence and metastases make them suffer and eventually yield to the disease through intrinsic (*denovo*) and extrinsic (acquired) chemo-resistance. The complications like chemo-resistant cancers can be overcome with the help of new therapeutic drugs and approaches, the current need of the hour (Nigjeh *et al.*, 2018). Table 3 illustrates triterpenoids isolated from different plants.

Naturally occurring phytochemicals:

Recent developments in research have led to the development of medicinal applications for naturally occurring and synthetically produced phytochemicals, which can decrease tumour growth both *in vitro* and *in vivo*. The anti-oxidant, anti-proliferation, and pro-apoptotic qualities of several of these are beneficial to treating different forms of cancer (Wang *et al.*, 2012). For cancer treatments, the naturally occurring novel anticancer agents from plant sources are promising. These plant derived products have a wide clinical application for treating cancers (Safarzadeh *et al.*, 2014). There are variety of molecules present in the crude samples extracted from the plants, namely, alkaloids, flavonoids, flavones and phenolic compounds with high capacity to kill cancer cells by nature (Patel and Patel, 2016).

Phytotherapy:

According to a 2015 report (Stinchcombe,2005), endocrine therapy has been shown to increase cancer patients' chances of survival. In cancer therapy apoptosis plays a vital role. The cancer cells show resistance towards apoptosis due to the suppression of apoptotic proteins and activation of anti- apoptotic proteins. There are various approaches to trigger and stimulate the process of apoptosis in which certain anticancer drugs come into action (Goldar *et al.*, 2015). The tumor initiation, growth and metastases are often due to abnormal iron metabolism. Samples collected from cancer patients show abnormally high iron levels. The other therapeutic approach towards breast cancer can be invention of drugs to decrease in the expression of feroportin and increase in the expression of lipocalin 2. Due to the aggressive features of the invasive breast cancer, it can be difficult to treat (Jia *et al.*, 2016). Malignant circumstances suggest that the early detection and controlling them can be a vital key point in the breast cancer therapy. Research suggests that the late detection of the disease serves as an element of the devastating surprise. Peptides play an important role in early diagnosis of cancer and promise superiority due to the specificity, unlike other therapeutic approaches (Xiao *et al.*, 2015). In the present treatments for breast cancer, there are immunotherapy with antibodies and peptide vaccines which have been proven to be effective for chemotherapy-resistant cancers (Wright, 2012). Some of the proteins that are used in the treatment of breast cancer are-- p5 (Mansourian *et al.*, 2014), SU18 and SU22 (Ohtake *et al.*, 2014), E75 (Mittendorf *et al.*, 2014) and ErbB-2 (Gil *et al.*, 2014). The ERBB2 targeted therapies involves Trastuzumab, Pertuzumab, Prastuzumab-Dmi,Lapatinib which is a ATP competitive EFGR/ERBB2 Inhibitors (Stuchmiller *et al.*, 2015).

Triterpenoids:

Table 3: List of triterpenoids isolated from different plants

Indian medicinal plant	Plant part	Type of triterpenoid	References
Abelmoschus esculentus	Plant Exudate	Oleanane	National Institute of Science Communication (2000)
Abutilon indicum		-	Khare (2008)
Adiantum caudatum	Frond	Fernane	Pastogi
Ailanthus triphysa	Bark, Root	Lupane	Khare (2008)
Albizia lebbeck	Flowers	Oleanane	Khare (2008)
Arundo donax	Leaf	-	Khare (2008)
Avicennia officinalis	Bark, Leaf	-	The Ayurvedic pharmacopedia of India: formulations
Azadirachta indica	Fruit, Leaf, Seed Kernels	Euphane	The Ayurvedic pharmacopedia of India: formulations
Baliospermumsolanifolium	Root	-	Majeed *et al.* (2014)
Buchananiacochinchinensis	Bark, Leaf	-	Khare (2008)
Cajanus cajan	Root	-	Khare (2008)
Castanea sativa	Leaf, Stem Bark	Oleane	Khare (2008)
Clerodendrum indicum	Flower, Root	Oleane	Khare (2008)
Crinum asiaticum	Bark	-	Khare (2008)
Diospyros exsculpta	Bark, Twigs	Lanostane	The Ayurvedic pharmacopedia of India: formulations
Diospyros malabarica	Bark, Fruit		Khare (2008)
Euphorbia neriifolia	Arieal parts	Lanostane	Khare (2008)
Euphorbia royleana		Oleane	Khare (2008)
Euphorbia thymifolia		Oleane	Khare (2008)
Euphorbia tirucalli	Plant Exudate	Tirucallane	Khare (2008)
Feronia limonia	Leaf, Stem	-	Khare (2008)
Ficus lacor	Leaf	-	Khare (2008)
Gardenia jasminoides	Flower, Fruit	Oleane	Wealth of India, Khare (2008)
Glycyrrhiza glabra	Root	Oleane	Khare (2008)
Grewia tenax	Bark	-	Khare (2008)
Grewia tiliifolia	Bark, Root	-	Khare (2008)
Imperata cylindrica	Root	Isoarborinol	Khare (2008)
Lagerstroemia speciosa	Leaves	Ursane	Patel and Patel (2016)
Mangifera indica	Bark	Cycloartane	Wang *et al.* (2012)
Melochiacorchorifolia	Aerial Part	Squalene	Khare (2008)
Pergulariadaemia	Whole Plant	-	Khare (2008)
Periploca calophylla	Stem	Ursane	Khare (2008)
Phyllanthus acidus	Fruit	Lupane	Khare (2008)
Pistacia chinensis	Seed	Lanostane	Khare (2008)
Rotheca serrata	Bark	Oleane	Khare (2008)
Scoparia dulcis	Whole Plant	Oleane	Khare (2008)
Shorea robusta	Bark	Ursane	Khare (2008)
Sorbus aucuparia	Bark, Leaf, Stem	Squalene	Khare (2008)
Toona ciliata	Bark	Tirucallane	Khare (2008)

Table 4: Classification of triterpenoids

Type of cyclic compound	Group
Acrylic	Sqalane
Monocyclic	Achilled A
Bicyclic	Pouoside A
Tricyclic	Lansioside A
Tetracyclic	Lanstone, Dammarane, Euphane
Pentacyclic	Oleanane, Ursane, Lupane, Hopane
Miscellaneous	Fernane

Triterpenoids are the largest subfamily, classified based on their pentyl count, among the structurally diverse family of secondary metabolites Isoprenoids. There are more than 14,000 structures reported so far (Almeida *et al.*, 2020). Most of the triterpenoid compounds consists of 30 carbon atoms and are composed of 6 isoprene units of mevalonic acid or deoxy-xylulose phosphate (Alqahtani *et al.*, 2013). According to Xu *et al.* (2017) the triterpenoids can be classified based on their basic carbon skeleton (Table 4).

The majority of chemical compounds derived from naturally occurring plant materials are pentacyclic triterpenoids, which can be found as free acids, esters, or glycosides (saponins) materials (Rhourri-Frih *et al.*, 2012). Many medicinal herbs used in the Chinese medicine contains Pentacyclic triterpenoid compounds (Xu *et al.*, 2017). Marine sponges, vegetables, fruits, cereals and spices are some of the common sources of triterpenoids (Colorado *et al.*, 2013).

The various application of triterpenoids are, surface waxes, specialized membrane compounds and signaling molecules (Wang *et al.*, 2010). The triterpenoids act as a defensive mechanism against pathogens and xenobiotics (Sun *et al.*, 2019). Triterpenoids have various biological properties like, hypoglycemic (Indu *et al.*, 2021), immunomodulatory, neuro-protection, Anti-parasitic (Hill and Connolly, 2017), anti-herbivore, insecticidal activities (Sun *et al.*, 2019), Anti-inflammatory (Yadav *et al.*, 2010), Anti- oxidant (Wang *et al.*, 2010, Kim *et al.*, 2012), anti- tumor (Kumar *et al.*, 2019), anti- proliferative (Memon *et al.*, 2015), Hepato-protective (Jiang *et al.*, 2017, Huo *et al.*, 2017), Cardiovascular (Quan *et al.*, 2016), and immunological adjuvant activities (Cruz *et al.*, 2016).

Cassia fistula:

Cassia fistula belonging to the Fabaceae family, has been used in the folklore medicine in different parts of South Asian countries and are native to Mexico, South Africa, India and Brazil (Antonysamy *et al.*, 2019). *C. fistula* is known for its wide range of pharmacological properties and in the practices of Unani and Ayurveda it is known as Argawadha also meant as “disease killer” (Sandeep Kaur *et al.*, 2020). Table 5 gives a detailed view of different compounds isolated from different parts of *C. fistula*.

WNT pathway:

WNT pathway is the most conserved pathways during evolution, embryonic development, adult tissue homeostasis and pathogenesis in variety of human cancers (Lim *et al.*, 2009). The WNT signaling network controls stemness in human malignancies such as breast, colorectal, gastric, and lung cancers by coordinating the actions of immune, endothelial, and cancer-associated fibroblasts in the tumor microenvironment (Katoh and Katoh, 2022). The WNT proteins are the major components of WNT pathway, they activate cell membrane receptors (paracrine or autocrine manner). The WNT proteins from the cells are responsible for the activation of transcriptional factors, intracellular proteins and frizzled proteins (FZD) which are induced by the cellular

Table 5: List of Phytocompounds isolated from different parts of *Cassia fistula*

Plant part	Compound isolated	References
Bark	1-Hexacosanol	Gupta and Tandon (2004)
	3,4-Dihydro-2-(4-hydroxyphenyl)-2h-1-benzopyran-3,4,7,8-tetrol	Kacera (2007)
	Anthraquinone	The Ayurvedic Pharmacopedia of India (2006)
	Barbaloin	Gupta and Tandon (2004)
	Beta-D-Glucose	Chatterjee and Prakashi (2005)
	Beta-Sitosterol	Gupta and Tandon (2004)
	Cianidanol	Chatterjee and Prakashi (2005)
	Leucodelphidin	Council of Scientific & Industrial Research (India) (1992)
	Lupeol	Gupta and Tandon (2004)
	Rhein	Gupta and Tandon (2004)
Flower	1-Docosene	Essien *et al*. (2018)
	1-Eicosene	Essien *et al*. (2018)
	1-Hexacosanol	Kacera (2007)
	1-Octadecene	Essien *et al.* (2018)
	2-Heptadecanone	Essien *et al.* (2018)
	2-Tridecanone	Essien *et al.* (2018)
	6,10,14-Trimethylpentadecan-2-one	Essien *et al.* (2018)
	Asperglaucide	Gupta and Tandon (2004)
	Benzyl salicylate	Essien *et al.* (2018)
	Beta-Bisabolene	Essien *et al.* (2018)
	Beta-D-Glucose	Chatterjee and Prakashi (2005)
	Beta-Ionone	Essien *et al.* (2018)
	Beta-Sitosterol-beta-D-glucoside	Pastogi (1960)
	Cabreuva oxide B	Essien *et al.* (2018)
	Clitorin	Kacera W, 2007
	Eicosane	Essien *et al.* (2018)
	Elemicin	Essien *et al.* (2018)
	Eugenol	Essien *et al.* (2018)
	Farnesylacetone	Essien *et al.* (2018)
	Heptacosane	Essien *et al.* (2018)
	Hexadecan-2-one	Essien *et al.* (2018)
	Hexadecane	Essien *et al.* (2018)
	Isoelemicin	Essien *et al.* (2018)
	Kaempferol	Gupta and Tandon (2004)
	Kaempferol-3-O-glucorhamnoside	Kacera (2007)
	Leucopelargonidin	Gupta and Tandon (2004)
	Leucopelargonidin tetramer	Kacera (2007)
	Methyl linoleate	Essien *et al.* (2018)
	Methyl linolenate	Essien *et al.* (2018)
	Methyl palmitate	Essien *et al.* (2018)
	Methyl salicylate	Essien *et al.* (2018)
	Methyleugenol	Essien *et al.* (2018); Chatterjee and Prakashi (2005)
	Nerolidol	Essien *et al.* (2018)
	Nonacosane	Essien *et al.* (2018)
	Octadecane	Essien *et al.* (2018)
	Palmitic acid	Essien *et al.* (2018)
	Pentacosane	Essien *et al.* (2018)

	Pentadecane	Essien *et al.* (2018)
	Proanthocyanidin	Council of Scientific & Industrial Research (India) (1992)
	Rhein	Gupta and Tandon (2004)
	Stigmasterol	Gupta and Tandon (2004)
	Tricosane	Essien *et al.* (2018)
	Tridecane	Essien *et al.* (2018)
Fruit	(-)-Epicatechin	Pastogi *et al.* (1960)
	1,4-Dihydroxy-6,7-dimethoxy-3-methyl-9,10-dioxoanthracene-2-carboxylic acid	Gupta and Tandon (2004)
	1-Triacontanol	Gupta and Tandon (2004)
	26-Methylheptacosanoic acid	Gupta and Tandon (2004)
	Aloe emodin	Council of Scientific & Industrial Research (India) (1992)
	Anthraquinone	The ayurvedic pharmacopedia of India (2001)
	Barbaloin	Khare (2008)
	Beta-Sitosterol	Gupta and Tandon (2004)
	Butyric acid	Khare (2008)
	Chrysophanol	Council of Scientific & Industrial Research (India) (1992)
	Cianidanol	Pastogi *et al.* (1960)
	D-Fructose	Pastogi *et al.* (1960)
	D-Glucose	Pastogi *et al.* (1960)
	Emodin	Council of Scientific & Industrial Research (India) (1992)
	Ethyl butyrate	Khare (2008)
	Galactomannan	Gupta and Tandon (2004)
	Hentriacontan-16-ol	Gupta and Tandon (2004)
	Hentriacontan-2-one	Gupta and Tandon (2004)
	Oxalic acid	Khare (2008)
	Procyanidin B2	Wealth of India (2000)
	Rhein	Council of Scientific & Industrial Research (India) (1992)
	Sucrose	Pastogi *et al.* (1960)
	Tannic acid	Khare (2008)
	Tetracosanoic acid	Gupta and Tandon (2004)
	Triacontane	Gupta and Tandon (2004)
Leaf	(-)-Epiafzelechin	Chatterjee and Prakashi (2005)
	1-Docosene	Essien *et al.* (2018)
	1-Eicosene	Essien *et al.* (2018)
	1-Hexadecene	Essien *et al.* (2018)
	1-Octadecene	Essien *et al.* (2018)
	1-Tetradecene	Essien *et al.* (2018)
	2-Heptadecanone	Essien *et al.* (2018)
	2-Tridecanone	Essien *et al.* (2018)
	3,4-Dihydroxybenzoic acid	Chatterjee and Prakashi (2005)
	6,10,14-Trimethylpentadecan-2-one	Essien *et al.* (2018)
	Alpha-Terpineol	Essien *et al.* (2018)
	Anthraquinone	Council of Scientific & Industrial Research (India) (1992)
	Benzyl salicylate	Essien *et al.* (2018)
	Beta-Bisabolene	Essien *et al.* (2018)
	Beta-D-Glucose	Chatterjee and Prakashi (2005)
	Beta-Ionone	Essien *et al.* (2018)
	Cabreuva oxide B	Essien *et al.* (2018)

	Chrysophanol	Chatterjee and Prakashi (2005)
	Cianidanol	Chatterjee and Prakashi (2005)
	Cis-beta-Farnesene	Essien *et al.* (2018)
	Citric acid	Chatterjee and Prakashi (2005)
	Docosane	Essien *et al.* (2018)
	Eicosane	Essien *et al.* (2018)
	Elemicin	Essien *et al.* (2018)
	Ellagic acid	Chatterjee and Prakashi (2005)
	Eugenol	Essien *et al.* (2018)
	Farnesylacetone	Essien *et al.* (2018)
	Hentriacontanoic acid	Wealth of India (2000)
	Heptacosane	Essien *et al.* (2018)
	Heptacosanoic acid	Wealth of India (2000)
	Heptadecane	Essien *et al.* (2018)
	Hexadecan-2-one	Essien *et al.* (2018)
	Hexadecane	Essien *et al.* (2018)
	Isoelemicin	Essien *et al.* (2018)
	Kaempferol	Chatterjee and Prakashi (2005)
	Methyl linoleate	Essien *et al.* (2018)
	Methyl linolenate	Essien *et al.* (2018)
	Methyl palmitate	Essien *et al.* (2018)
	Methyl salicylate	Essien *et al.* (2018)
	Methyleugenol	Essien *et al.* (2018)
	Nerol	Essien *et al.* (2018)
	Nerolidol	Essien *et al.* (2018)
	Nonacosane	Essien *et al.* (2018)
	Nonacosanoic acid	Wealth of India (2000)
	Nonadecane	Essien *et al.* (2018)
	Octadecane	Essien *et al.* (2018)
	Palmitic acid	Essien *et al.* (2018)
	Pentacosane	Essien *et al.* (2018)
	Pentadecane	Essien E E et.al., 2018
	Physcion	Chatterjee and Prakashi (2005)
	Phytol	Essien *et al.* (2018)
	Procyanidin B2	Chatterjee and Prakashi (2005)
	Quercetin	Chatterjee and Prakashi (2005)
	Rhein	Gupta and Tandon (2004)
	Sennoside A	Gupta and Tandon (2004)
	Sennoside B	Gupta and Tandon (2004)
	Tannic acid	Wealth of India (2000)
	Tetradecane	Essien *et al.* (2018)
	Triacontanoic acid	Wealth of India (2000)
	Tricosane	Essien *et al.* (2018)
	Tridecane	Essien *et al.* (2018)
Plant cells/culture	Chrysophanol	Wealth of India (2000)
	Physcion	Wealth of India (2000)
Root	3,4-Dihydro-2-(4-hydroxyphenyl)-2h-1-benzopyran-3,4,7,8-tetrol	Council of Scientific & Industrial Research (India) (1992)
	beta-Sitosterol	Gupta and Tandon (2004)
	Betulinic acid	Gupta and Tandon (2004)
Seed	(9Z)-(12S,13R)-12,13-Epoxyoctadecenoic acid	Gupta and Tandon (2004)
	Galactomannan	Chatterjee and Prakashi (2005)
	Linoleic acid	Reviews on Indian Medicinal Plants (2004)
	Malvalic acid	Gupta and Tandon (2004)
	Oleic acid	Gupta and Tandon (2004)

	Palmitic acid	Gupta and Tandon (2004)
	Stearic acid	Gupta and Tandon (2004)
	Sterculic acid	Gupta and Tandon (2004)
	Sucrose	Chatterjee and Prakashi (2005)
Stem	3,4-Dihydro-2-(4-hydroxyphenyl)-2h-1-benzopyran-3,4,7,8-tetrol	Gupta and Tandon (2004)
Whole plant	(-)-Epiafzelechin	Kacera (2007)
	(-)-Epicatechin	Kacera (2007)
	Chrysophanol	Kacera (2007)
	Emodin	Kacera (2007)
	Kaempferol-3-O-glucorhamnoside	Kacera (2007)
	Phlobaphene	Kacera (2007)
	Procyanidin	Kacera (2007)
Wood	3,4-Dihydro-2-(4-hydroxyphenyl)-2h-1-benzopyran-3,4,7,8-tetrol	Kacera (2007)
	Aromadendrin	Gupta and Tandon (2004)
	Barbaloin	Gupta and Tandon (2004)
	beta-D-Glucose	Chatterjee and Prakashi (2005)
	Chrysophanol	Kacera (2007)
	Cianidanol	Gupta and Tandon (2004)
	Kaempferol	Gupta and Tandon (2004)
	Rhein	Gupta and Tandon (2004)

mechanisms. In the breast cancer metastasis up-regulation of Frizzled protein which is a major component in the WNT signaling pathway is found to be a potential prognosis marker. There are three signaling pathways which serve as a base for the WNT pathway: canonical β-catechin dependent, β-catechin independent, non-canonical WNT signaling pathways (PCP signaling and Ca^{2+} pathways) (Taciak *et al.*, 2018). The scaffold proteins Axin, APC, GSK3 kinase, and casein kinase (CK1) make up the destruction complex, which interacts with -catenin in the canonical pathway and phosphorylates in the absence of Wnt ligands (Wnt3a and Wnt1). This phosphorylation causes β-catenin to be ubiquitinated and degraded (Gupta *et al.*, 2021). When Wnt interacts to the frizzled (Fzd) receptors and/or the low-density lipoprotein related protein (LRP) co-receptors, this pathway is triggered. The signaling is passed on to the MYC, CCND1, LGR5, SNAI1, IFNG, CCL28, CD274 (PD-L1) and other target genes through the β- catenin- TCF/LEF- dependent transcription process. Disheveled (Dvl) proteins are engaged, which inactivate the destruction complex and cause β-catenin to stabilize and accumulate. This then moves into the nucleus, attaches to the T-cell factor (TCF) and lymphoid enhancer factor (LEF), facilitating the transcription of a number of target genes (Gupta *et al.*, 2021). Canonical WNT signaling, which also influences immunological tolerance and immune tolerance surveillance, causes CSCs that cycle quickly to proliferate (Sen, 2002).In contrast, Phospholipase C, Rac1, and RhoA receive non-canonical WNT signaling through Frizzled or the ROR1/2 receptors to modulate transcriptional outputs mediated by NFAT, AP-1, and YAP-TEAD, respectively (Sen, 2002). Through interaction with TGF (transforming growth factor) signaling cascades, noncanonical WNT signaling supports maintenance of slowly cycling, quiescent, or latent CSCs and promotes epithelial-mesenchymal transition, whereas the TGF signaling network results in immune evasion. The cross talk between WNT and TNF serve as a future perspective for the experimental analysis of the metastasis processes (Bell *et al.*, 2017). Research suggested that the driving force of mammary tumorigenesis in mice was WNT1 gene. The tumor suppressor genes tightly control the WNT pathway activity during tissue homeostasis, either as a core component or act in negative feedback loop (Bugter *et al.*, 2021). In variety of cancer types the mutation or silencing of the WNT tumor suppressor gene has

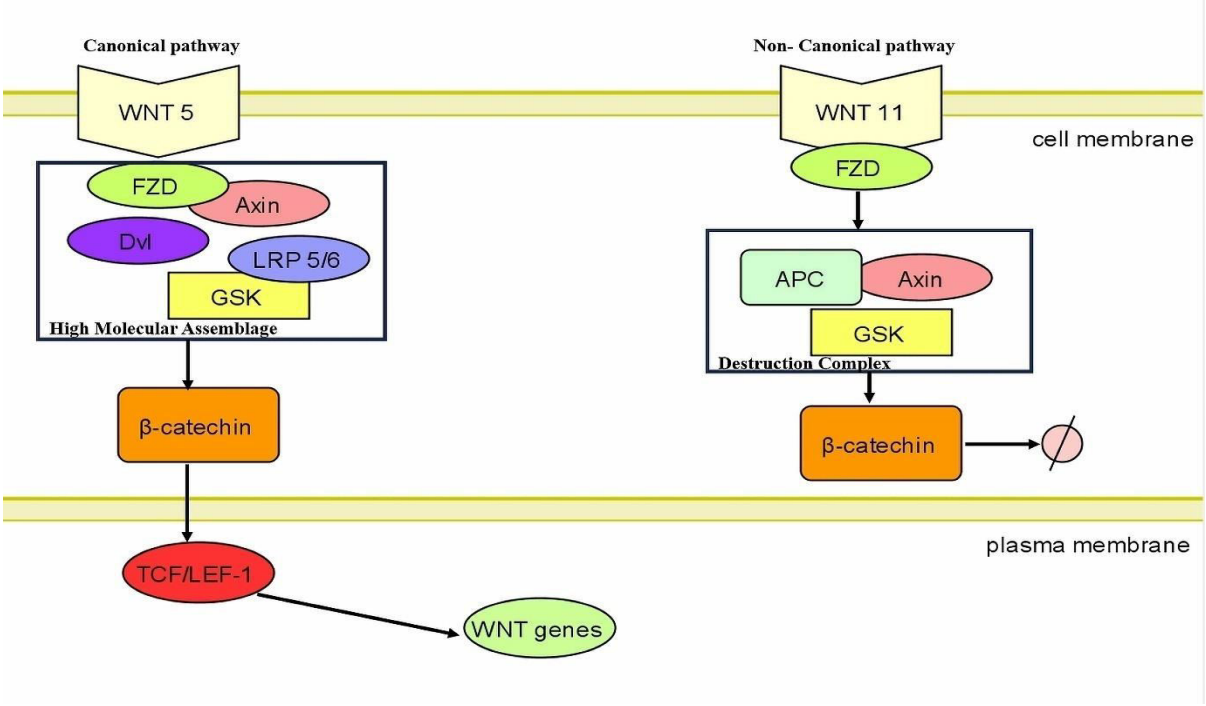

Fig. 2: Proposed possible WNT Pathway.

been reported to occur frequently (Polakis, 2012). With constant activation of the β- catechin pathway the cancer cells gain the ability to self-renewing and growth properties which are linked to resistance towards therapy. Mixture of deletion, missense mutations, non-sense mutations and frameshift mutations in the tumor suppressor genes are observed throughout the length of the gene making it difficult to interpret (Bugter *et al.*, 2021). Figure 2 depicts the detailed canonical and non-canonical pathways involved in WNT pathway.

Conclusion

Topping the charts of mortality, breast cancer leads the way as a very serious disease among women of all nationality. The definite need for an alternative and efficient way of detecting and treating the malignancy at the early stage can provide the patients with a longer period of survival. Hence, the need for a novel approach with less side-effects and no associated complications has arised in order to overcome the chemi-resistance of the breast cancer. In this review the alternative therapies for various cancer were summarized and different aspects of triterpenoids, including the sources, applications and treatment possibilities was discussed, along with the information about the compounds isolated and different therapeutic parts of the plant *Cassia fistula* was briefed. The biomarkers and WNT pathway associated with the initiation, diagnosis and treatments of Breast cancer and metastatic breast cancer was also discussed. As a result, the creation of novel triterpenoids from the plant has the potential to be an effective anti-cancer medication for breast cancer cell lines. Though the phytochemicals can be natural enhancers they can still be not affordable to people of all social statuses which can lead to the development of synthesis of small molecule(s) synthetically using combinatorial chemistry based on the novel triterpenoids can be a game changer in the pharmaceutical field.

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