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REVIEW PAPER

Lectin: A Molecular Tool in Cancer Diagnosis and Therapy with Special Reference to Reproductive Cancers

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Abstract

The prevalence of cancer deaths globally and domestically is higher especially due to the deferment of diagnosis and lack of facilities for women's reproductive cancers. The present review focussed to explore the application of lectins in cancer theranostics. Though there is cancer diagnostic and treatment available there is no promising early diagnostic tool and effective treatment available for the cancer which is the major concern. Lectins are cellulose-binding proteins that are strongly determined in saccharide groups of glycans, glycopeptides, or glycolipids. In the concomitance of events in cells, carbohydrates, and proteins, lectins play an important role. Lectins bind superiorly to the cancer cell membrane and their receptors induce the cytotoxic effect, which results in caspase-mediated cell death, and prohibits tumour development. Lectin snuffing also reveals polyamine stocks and impedes the growth of cancerous cells. They affect the cell cycle by non-apoptotic aggregation, seizure of the cell cycle phase G2, M, and the mediation of caspases. It can also adversely affect the action of telomerase and hinder vascularisation. They promote immunomodulation and adversely limit protein synthesis. Their easy availability and its characteristics support its use in cancer diagnosis and therapy, despite their small corollary effects. Future investigations recommend focussing more on the key applications of lectin by reducing its concurrent effects and carrying out more in-vitro investigations. However, the use of lectin formulations for cancer theranostics is a new area in cancer detection and treatment. In this review, plant lectin appears to be a potential target for cancer research in the fields of diagnosis and theranostics.

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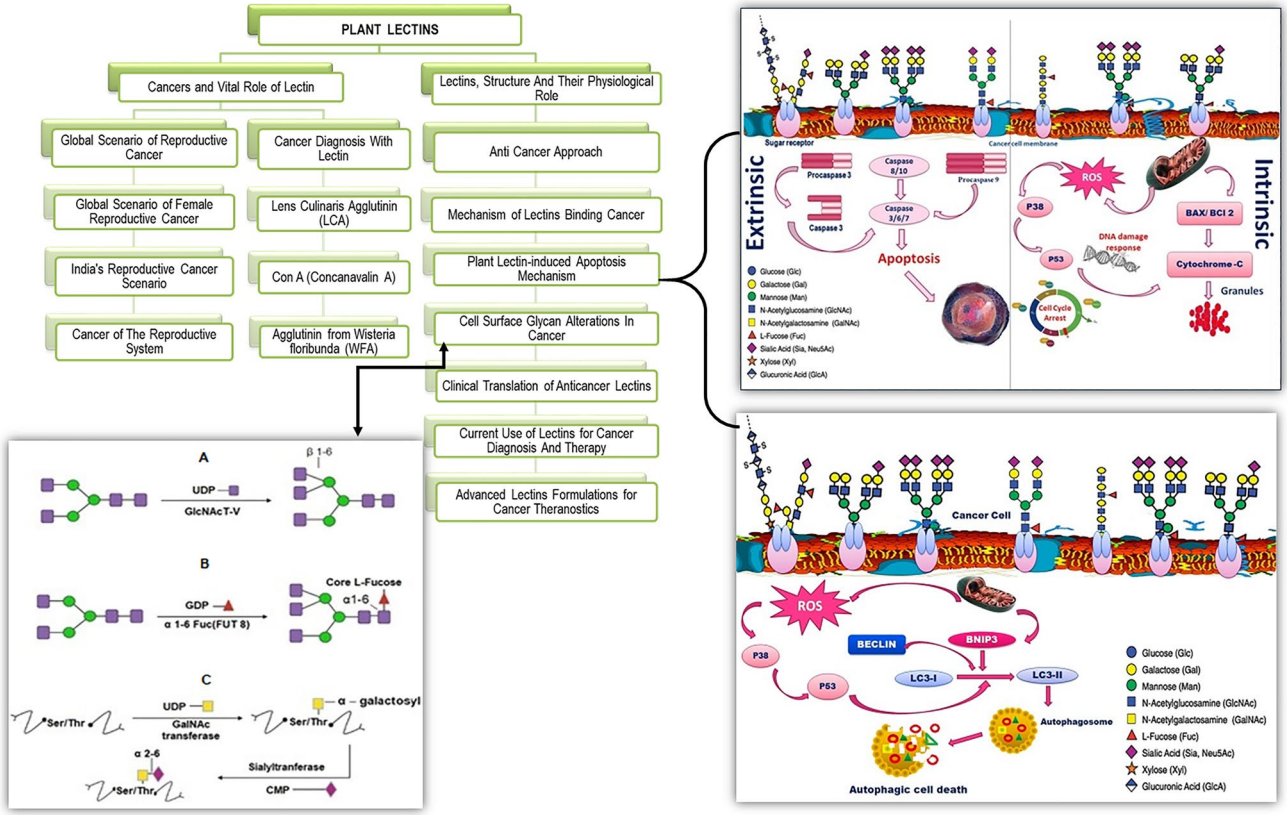
Graphical Abstract



Keywords Anticancer lectins · Glycosylation · Reproductive cancers · Surface markers · Therapeutic agents · Theranostics

Introduction

Worldwide, the reported leading cause of death is cancer, accounting for nearly one in six or nearly 10 million deaths in 2020 [1]. The higher rate of cancer death may be due to the late diagnosis and lack of effective treatment.

Plant lectins have increasingly garnered considerable attention because of their ability to accurately target cell membrane glycans, which might be useful in a range of fields [2]. Plant lectins have been used as scientific tools for glycan detection and characterisation because they are carbohydrate-binding proteins that reversibly interact with particular carbohydrates in glycoconjugates [3]. Every living organ's cell and plasma membrane contain lectins, which are glycan-binding proteins. Furthermore, lectins play roles in immunological defence, cell migration, cell-to-cell contacts, morphogenesis, organogenesis, and inflammation [4, 5]. Plant lectins may have a role in cancer development and therapy by inhibiting cell death pathways [2]. Though there are cancer diagnostics and treatments available, there is no promising early diagnostic tool and effective treatment available for cancer, which is the major concern. Early detection (early diagnosis and screening) and effective treatment are the means by which many cancers can be cured [1]. The present review focusses on exploring the application of lectins in cancer theranostics.

Lectins: Structure and Their Physiological Role

Lectins have a compact structure without an alpha-helix and beta-sheets that are anti-parallel in nature. In lectins, which may make up as much as 30% of the total protein and are expressed in different parts of the plant, such as modulation in roots, they also play a role in pathogen defence.

Characterising lectin-binding affinity and function has depended solely on the development of multiple probes as well as approaches for measuring static and dynamic adherence. Plant lectins have been employed in a wide range of applications, such as cell agglutination, blood typing, cell separation, and analysis. Simultaneously, it is valuable

in the classification and selection of malignant cells with changed glycosylation [3, 5]. It is also consigned for the detection of toxic conjugates for tumour-inducing apoptosis, cytochemical characterisation and staining of cells and tissues, and cell mutagenesis. Along with these applications, lectin-binding qualities are utilised in neurological pathway mapping, glycoconjugate purification, and glycan testing. The availability and uses of plant lectins in cancer were the subjects of this research. However, understanding the underlying facts about cancer is necessary to appreciate plant lectin applications and their function in cancer diagnosis and treatment [6].

Physiology of Cancer

The uncontrolled expansion of immortal cells is the fundamental flaw that leads to cancer. Cancer cells grow and divide uncontrollably instead of responding adequately to the cues that govern normal cell activity, infecting normal tissues and organs and subsequently spreading to other parts (metastasis). As a result of accumulating numerous cell regulatory systems, cancer cells show a wide lack of growth control. This is evident in many features of cell activity that distinguish cancer cells from normal cells. The primary cause of death from cancer is the widespread metastases [1].

Global Scenario of Cancer

As per the International Agency for Research on Cancer (IARC), one in every five people will get cancer at some point in their lives, with one out of every eight men and one out of every eleven women dying from it. According to the most recent estimates, around 50 million people develop cancer within five years of a previous cancer diagnosis. The ageing of the global population, as well as socioeconomic risk factors, continue to be major drivers of this rise [7].

Global Scenario of Female Reproductive Cancer

The IARC released the updated Globocan 2020 study on December 14th, 2020, estimating a global cancer burden of 19.3 million cases and 10 million cancer deaths in 2020 [8]. Bray et al., 2012 stated that rapid societal and economic transition may lead to a decrease in infection-related cancers, which is counterpoised by a higher number of cancers related to reproductive, dietary, and hormonal factors [9]. Female reproductive system cancers, which include the cervix, uterus (cervical cancer), vulvar, corpus uteri (which includes mostly endometrial adenocarcinomas and some other rarer cancers such as sarcomas), ovarian, vaginal, oviduct, and choriocarcinoma, are a major cause of cancer deaths worldwide. [10]. Among them, ovarian cancer is found to have a higher rate of malignancy, mainly due to its asymptomatic nature. It is considered the 18th most deadly disease worldwide, and relative survival is found to be approximately 45% [11]. According to research, the majority of ovarian carcinomas are caused by ovarian germinal epithelium or postovulatory epidermoid cysts developed following follicular rupture and healing. [12]. The risk of developing ovarian cancer in women's lifetimes is found to be 1 in 75, and its ratio was found to be high in developing countries [13, 14]. The highest cases of ovarian cancer were registered in the USA (81% of all cases), China (14.6%), and India (11.3%), and similar trends were also noticed in Asian countries like Singapore, Brunei, and Kazakhstan [15]. Data from Bangladesh highlight that breast cancer (32.8%) has the highest prevalence among females, followed by cervical (26.1%) and ovarian cancer (3.3%) among reproductive cancers [16]. However, a cross-sectional survey revealed the prevalence of different types of cancer in Bangladesh, with ovary (39%) and breast (27%) cancer among females [17]. Breast cancer was the most prevalent cancer in women globally in 2020, accounting for 25.8% of all new cases diagnosed, with 2,261,419 cases reported. Breast cancer (24.5%), colorectal cancer (9.4%), and lung cancer (8.4%) accounted for 42.3% of all new cancer diagnoses, excluding non-melanoma skin cancer. Cervical cancer was the fourth most common malignancy among women, accounting for 6.5% of all new cases diagnosed as depicted in Fig. 1 [8].

India's Reproductive Cancer Scenario

According to national cancer registry data, the most common cancer sites for women are cervical, uterine, breast, and oral cancers. In India, the four bodies: cervical cervix uteri, breast, corpus uteri, and ovaries are commonly associated with 50–60 percent of cancers in women. More than 70% of most women report advanced-stage diagnosis and treatment, which results in poor health and a high rate of mortality. Over 70,000 new cervical uterus cases (70,000), out of which ovarian (3–8%), corpus uteri (0.5–4.8%), vulvar, and gestational trophoblastic (1–3%) have been documented in India. The National Cancer Control Programme in India emphasises the significance of early detection and intervention. The majority of Indian women are unaware of their ailment and have little access to preventative measures or treatment. Although cancer screening programmes such as pap smears and colposcopy are available in all regional cancer centres and hospitals, population coverage is restricted. In India, almost 70% of the population lives in rural regions with poor health and livelihoods. Early marriage, early pregnancy, co-morbidities, inadequate genital hygiene, and sexually transmissible chronic illnesses are all risk factors for cervical cancer in rural women [18].

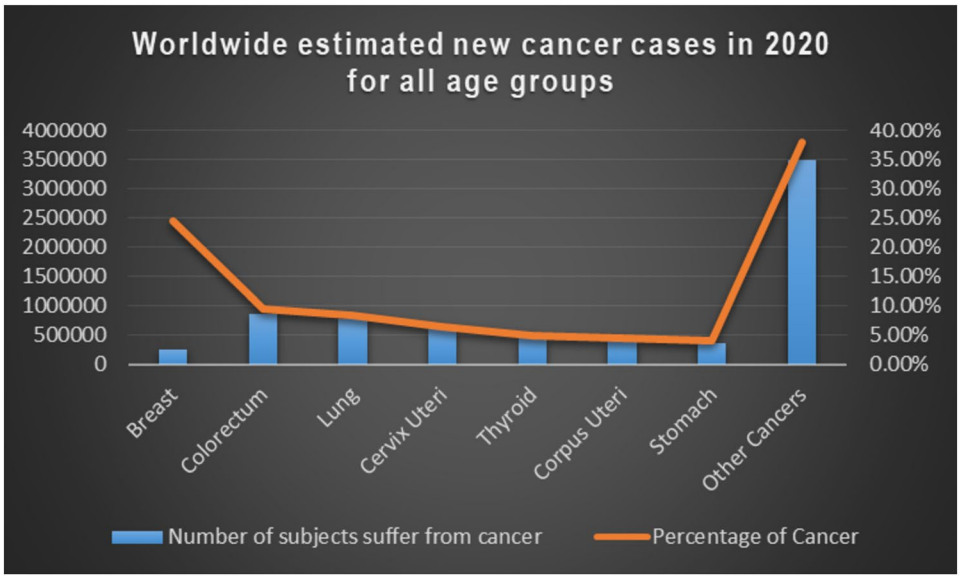


Fig. 1 A comprehensive overview of global new female cancer cases in 2020

Cancer of the Reproductive System

Cervical, ovarian, uterine, vaginal, and vulvar cancers are the five most prevalent forms of gynaecologic malignancies recorded. Fallopian tube carcinoma is a kind of gynaecologic cancer that is rather uncommon [19]. Breast cancer is the most common cancer that kills women worldwide. Cancer risk increases in postmenopausal women with early menarche, late menopause, and obesity. Although alcohol increases the risk, physical activity is likely to reduce it. Childbearing lowers risk, with a higher level of protection for the first child [10]. Cervical cancer is a serious public health problem that affects over 500,000 women each year throughout the world. It is most common in developing countries with insufficient screening processes. Human papilloma virus (HPV) infection, smoking, and immune system dysfunction are all risk factors. The majority of women with early-stage malignancies can be treated, although there is a high rate of treatment-related long-term morbidity [20]. Ovarian cancer is a compilation of at least five discrete histological subtypes, rather than a single disease. Cytoreductive surgery and platinum-based chemotherapy are the standard therapies currently offered for newly diagnosed cancers. The most common kind of ovarian cancer is high-grade serous carcinoma. At the time of diagnosis, it responds well to platinum-based chemotherapy. It usually recurs and becomes increasingly resistant to treatment [21]. With almost 1.5 million new cases reported in 2012, uterine cancer is the sixth most prevalent cancer in women and the 14th most common disease worldwide. In 5% of female cases and 2% of total cases, this rise is most likely attributable to rising obesity, longer life expectancy, and the use of tamoxifen as a breast cancer adjuvant. Endometrial cancer is the only cancer that affects women; vaginal cancer is an uncommon malignancy that accounts for just nearly 3% of all gynaecological malignancies [22]. This is because primary vaginal cancer can migrate from the cervix, vulva, and other metastatic cancers to the vagina, so it needs to be treated cautiously.

High-risk HPV strains can increase the risk of some reproductive malignancies, including cervical, vulvar, and vaginal cancer. The risk of breast cancer in women is intimately linked to their exposure to ovulatory hormones such as oestrogen and progesterone. Early menstruation, late menopause, and hormonal supplements that postpone conception and disturb the duration and level of exposure in the normal hormonal cycle are associated with an increased risk of breast cancer. Pregnancy and breastfeeding, on the other hand, which shorten a woman's lifelong menstrual cycles, hence decreasing cumulative hormone exposure, have been associated with a lower risk of breast cancer. Furthermore, these actions cause breast cells to develop and differentiate, potentially making them more resistant to cancer cell transformation. If the pregnancy has an inherited faulty BRCA gene, a history of breast or bowel cancer, or prior radiation treatment for another cancer, the risk of ovarian cancer may increase [23, 24].

The Federation Internationale de Gynecologie et d'Obstetrique (FIGO) uses the same recommendations for vaginal cancer staging as it does for cervical cancer. FIGO encourages the use of advanced imaging modalities to help in therapy [25]. In 2018, 6190 new cases of vulvar cancer were predicted to be diagnosed, equivalent to 0.4 percent of overall cancers. With a median age at onset of 68 years, this is primarily an elderly sickness. The prevalence of vulvar cancer has grown by 0.6 percent per year on average over the last 10 years, yet relative survivability appears to be dropping. Squamous cell carcinoma (SCC) accounts for

more than 90% of vulvar cancer cases. Dysplastic lesions are generally present before SCC. Melanoma is the second most frequent type of vulvar cancer after cervical cancer. The remaining cancers include adenocarcinoma, basal cell carcinoma, sarcoma, and undifferentiated carcinoma [26]. The above-mentioned kind of reproductive cancer in women, as well as the way in which lectin binds cancer cells, are examined in greater depth in a subsequent review.

Mechanism of Cancer Binding Lectins

Plant Lectin-Induced Autophagy

Autophagy, a stress-response cellular activity, has been studied for decades. When cells are stressed by food deficiency, oxidative conditions, or injury, autophagy acts as a degrading mechanism for the damaged cell, elimination of potentially toxic components [27]. There are three forms of autophagy in eukaryotic cells: macroautophagy, microautophagy, and chaperone-mediated autophagy [28]. Briefly, three types of autophagy have been identified in eukaryotic cells (i) macroautophagy: In this, the cell forms a phagophore by forming a bilayer membrane to sequester the cell, digests the cell debris, and other toxic by-products in vacuoles or lysosomes into simple forms that are reused by the cell as raw material for the production of various cell products; (ii) microautophagy: In this, the cytoplasmic remains are internalised into the lysosomes, resulting in the formation of microautophagic bodies that are directly taken up and digested by lysosomal enzymes into simpler products; and (iii) chaperone-mediated autophagy. In this, heat shock protein (71 kDa), chaperones directly bind to the KFERQ motif of the substrate and are taken for embattle with the lysosomes for the breakdown into non-toxic products [28–31]. Autophagy is a key way for tumour cells to commit suicide, not only as a survival reaction to a growth factor or a lack of nourishment as mentioned in Fig. 2 [32]. Furthermore, recent studies have found that mammalian cell death is involved in the co-regulation of apoptosis and autophagy [33, 34]. Surprisingly, some recent research have found comparable above-described properties in lectin-induced apoptosis [35–37].

Plant Lectin-Induced Apoptosis Mechanism

Various biological signalling mechanisms for tumour cells are aware of apoptosis. It is among the most substantial molecular pathways, wherein cancer is intimately connected to programmed cell death (PCD) or apoptosis [38, 39]. A strong plant lecture technique is to manipulate the cell's major molecular constituents as depicted in Fig. 3 [40, 41]. As a result, apoptosis modulation has been discovered for molecules or pathways that are important in reducing

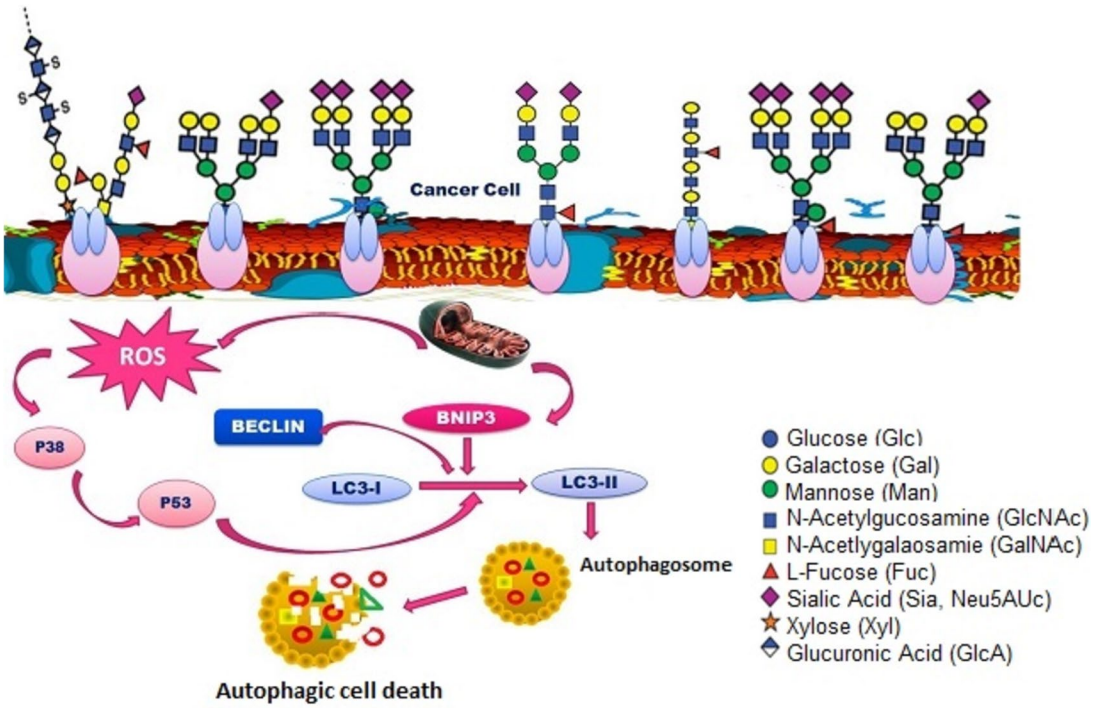


Fig.2 Molecular pathways of plant lectin-mediated autophagy in tumour cells mediated by mitochondrial BNIP3 and/or the ROS-p38-p53 pathway

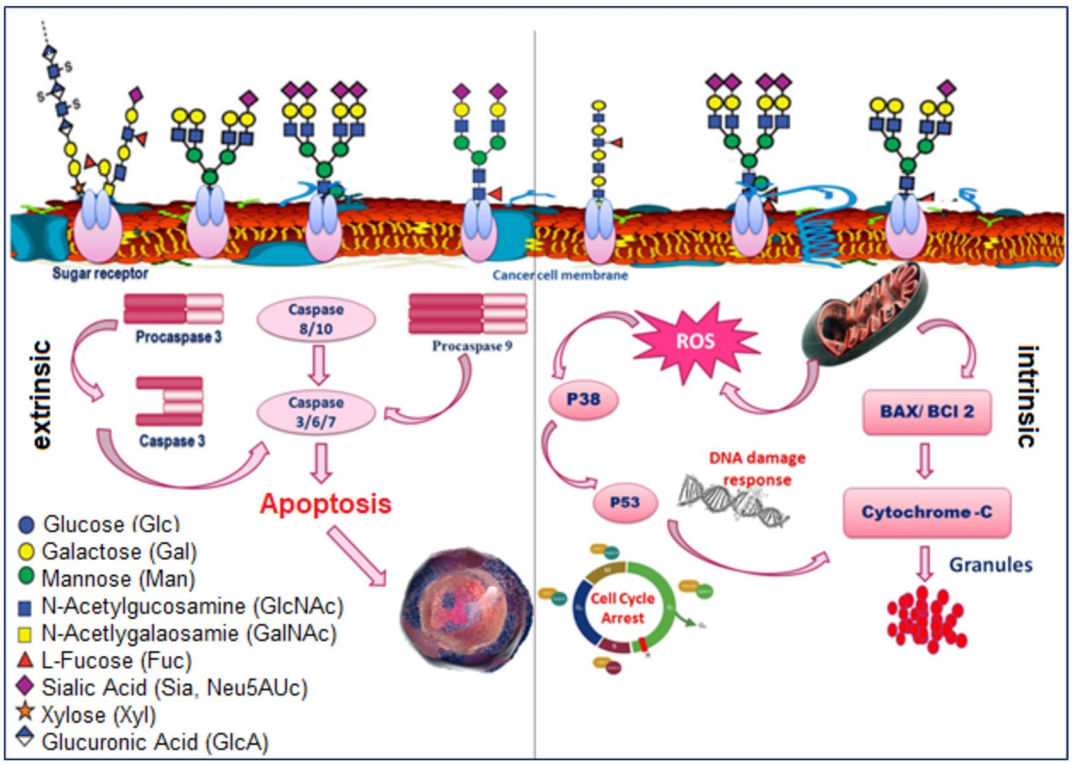


Fig. 3 Plant lectin-induced apoptosis mediated through mitochondrial death-receptor pathways

carcinogenesis. With the importance of lectins, a new target for cancer therapy may emerge [35].

Cell Surface Glycan Alterations in Cancer

Glycoproteins, lipids, and glycosaminoglycans form the glycocalyx, a peculiar carbohydrate covering. Glycoproteins, proteoglycans, and glycosphingolipids (GSLs) are all regularly found with N-linked and O-linked glycans attached (GAGs), which are O-linked towards the protein core and are also found in the glycocalyx as depicted in Fig. 4 [35, 42, 43]. The shift in glycocalyx structure from a physiological to a sick state is the core concept in many lectin-based illness diagnoses. Even though these phenomena were poorly understood in the early 1970s (while they were first described), current advances in glycosciences, genomics, proteomics, and mass spectrometry allow for the accurate recognition of differences in glycan structural composition, as well as between diseased and normal status of cells. Cancer has well-documented changes in the cell surface glycosylation during malignant transformation, tumour cell differentiation, and metastasis [44, 45].

In cancer, higher expression of cancer-related carbohydrate markers such as Thomsen–Friedenreich (TF) and sialyl Lewis A/X antigens was associated with increased UDP-Gal transporter mRNA expression. Although no significant variations in mRNA levels of uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) and cytidine monophosphate sialic acid (CMP-SA) in malignant and non-malignant colon tissues were found in the investigation, UDP-GlcNAc has been linked to cancer in various studies [46]. In addition, a decrease in GlcNAcT-V enzyme activity is linked to a reduction in the metastatic phenotype [47]. One of the most prevalent glycan changes linked to cancer is fucosylation, or even the conversion of fucose residue to oligosaccharides connected to proteins or lipids. During carcinogenesis, glucosyltransferases, guanosine diphosphate (GDP)-fucose production enzymes, and the GDP-fucose transporter are the main regulators of fucosylation [48]. Removing the FUT8 gene from aggressive cancer cell lines dramatically lowers cancer cell growth, metastasis, and tumour formation, according to Chen et al., L-fucose was found to be overexpressed in cancers, including ovarian carcinoma, colorectal adenocarcinoma, and others [49, 50]. In human hepatocellular carcinoma, fucosylation biosynthesis was revealed to be active. It has been demonstrated to be regulated by increased GDP-L-fucose synthase (FX protein) expression, followed by a rise in GDP-L-fucose and 1,6-fucosyltransferase (1–6) expression [51, 52]. As a consequence, Listinsky et al. argued for the use of defucosylation as a specific ablation therapy for a variety of human malignancies. Yuan et al. tested this notion further by

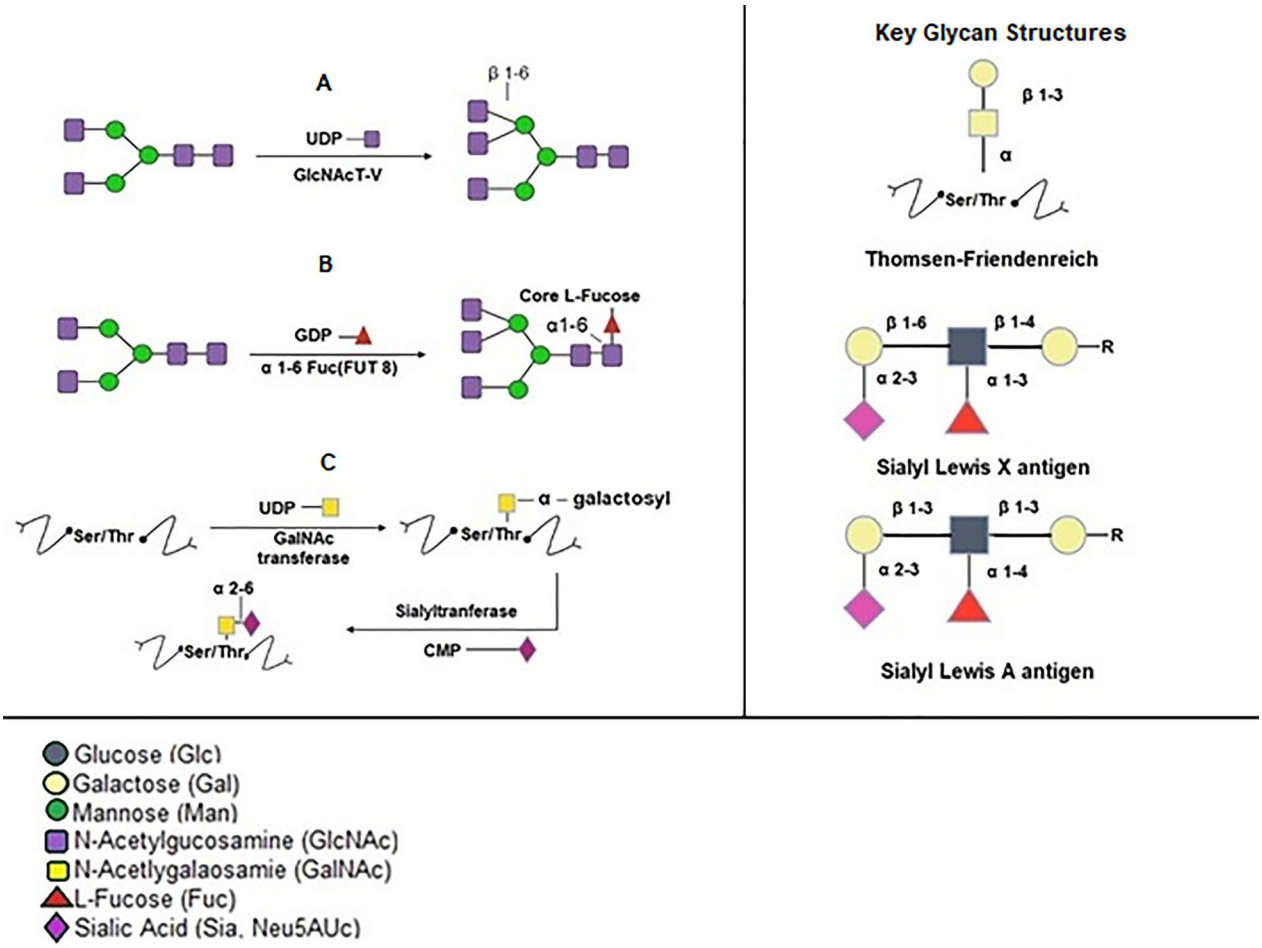


Fig. 4 The major glycosylation reactions (A, B, and C) in cancer, as well as key glycan structures

using L-fucosidase, a glycosidase that preferentially removes L-fucose, to treat human breast cancer MDA-MB-231 [53]. Although fucosidase therapy had little effect on MDAMB-231 cell proliferation or survival, it did significantly diminish cancer cell invasion by lowering cell surface levels of CD44 and CDIS [54]. More specifically, L-fucose has been suggested as a possible need for the growth of malignancy and metastatic characteristics in several human breast cancers [55].

Increased sialylation levels in cancer cells are hypothesised to enhance disease development by shielding cancer cells from apoptosis, increasing metastasis, and giving treatment resistance [56, 57]. Increases in 2–6 linked sialic acids attached to the outer N-acetyllactosamine (Gall-4GlcNAc) units or the inner GalNAc1-O-Ser/Thr units on O-glycans are common indicators of increased sialylation [58]. Human cancer development, metastatic spread, and poor prognosis have all been linked to this sialylation alteration [59]. Despite this, alpha-2, 3-sialic acid has been proven to play a significant role in cancer formation. Cui et al. observed that the highest levels of alpha-2, 3-sialic acid residue expression in breast cancer are linked to metastatic potential [60]. Most immune cells include sialic acid-binding Ig-like lectins (Siglecs), which can deliver inhibitory signals when attached to sialic acid [61]. It has been suggested that altering tumour cells' sialylation might affect their interactions with specific signals, increasing tumour development. Similarly, hypersialylation of the Fas receptor (apoptosis antigen 1) inhibits apoptosis activation in cancer cells while not affecting agonist binding. The activation of the death-inducing signalling complex (DISC) is blocked by alpha-2–6 sialylation of Fas by the sialyltransferase ST6Gal-I, which prevents the Fas-associated adaptor protein (FADD) from connecting to the FasR death domain [56, 62].

Cancer Diagnosis with Lectin

Plant lectins have generated interest due to their anticancer qualities and prospective use as anti-tumour drugs. They are hypothesised to be capable of binding directly to cancer cell membranes or receptors, eliciting cytotoxicity, apoptosis, autophagy, and tumour growth inhibition. These are some

of the non-reproductive malignancies for which lectins are used in therapy and diagnostics; lectins can also be found in reproductive tumours.

Concanavalin A (Con A) Lectins and Cancer Diagnosis

Con A is seen to be helpful in the diagnosis of some liver illnesses [63, 64]. The serum reactive species of a-fetoprotein (AFP) was much lower in patients with liver metastases than in those with hepatocellular carcinoma (HCC) or benign liver disease [65]. HCC patients had significantly greater plasma concentrations of Con A-binding cathepsin D [66]. When comparing non-cirrhotic and cirrhotic controls, a Western blotting study for procathespsin D protein expression in HCC indicated 4.3- and 2.3-fold increases, respectively. Con A stained HCC cells differently than normal tissues [67]. Recent advancements in the use of Con-A-magnetic particles may pave the way for new HCC-specific biomarkers to be discovered [68]. Peroxidase labelling was found to be effective in differentiating exfoliated uterine epithelial cells between normal and cancer patients, with statistical analysis revealing that at least 99% of all healthy people will have a labelling percentage above 45%, while cancer patients will have a labelling percentage below 30%. When the labelling percentage of 45% is used as a crucial threshold, the Con-A-HRP labelling may serve as an additional detection tool for uterine cervical cancer [69]. A study from Elshal et al. (2022) showed that combined treatment of Con A and Tamoxifen inhibited the cell viability of MCF7 cells (breast cell line) via induction of G1 phase arrest and reduced cyclin D1 activity, and on the other hand, upregulated apoptosis and autophagy [70]. As Con A is a potent lectin-based anticancer agent, it may be a promising marker in the case of reproductive cancer [71].

Wisteria floribunda (WFA) Lectins and Cancer Diagnosis

The combination of WFA-reactive LI-binding proteins and the WFA-reactive sialylated tumour-associated mucin-I assay has proven to be a valid serological standard test for cholangiocarcinoma [72]. Furthermore, because WFA-reactive ceruloplasmin levels are higher in ascites fluids from persons with epithelial ovarian cancer than in benign tissues, this protein might be utilised to diagnose ovarian cancer, namely clear cell carcinoma [73].

Agglutinin from WFA is widely used in the determination of hepatic carcinoma, cholangiocarcinoma, and reproductive cancers such as breast and ovarian cancer. The use of WFA as a diagnostic tool in serum has the advantage of very low background noise, as very small amounts of glycoproteins agglutinate with WFA [74]. A study from Agrawal et al., 2020 showed that extracts of WFA have antiproliferative properties on breast cancer cell lines MCF7, and this is attributed to the binding of lectins to the cell surface and the triggering of S and G2 phase arrest, induction of apoptosis by caspase-3, ROS generation, and LDH leakage [75]. Further, Tam therapy (tamoxifen-resistant breast cancer cells) showed increased binding to WFA compared to tamoxifen-sensitive cells, and it is mainly due to glycoproteins such as CD166 and Integrin beta 1. Therefore, in clinical samples, predominant WFA staining was noticed in tamoxifen-treated cells. As a result, WFA can be used as a predictive biomarker in the screening of oestrogen receptor-positive breast cancer patients [76].

In the case of ovarian cancer, epithelial ovarian cancer can be classified into clear cell, endometrioid, serous, and mucinous. Among them, clear cell carcinoma is relatively resistant to chemotherapy, and it is usually associated with endometriosis. Furthermore, lectin histochemistry demonstrated that WFA-binding glycans were reduced exclusively in the stromal components of ovarian endometriotic cysts, not in the epithelial components [77]. WFA-reactive ceruloplasmin (CP) was recently identified as a possible marker for ovarian clear cell carcinoma (CCC), with site-specific glycome analysis employing liquid chromatography/mass spectrometry revealing that WFA-CP from CCC binds to WFA via the GalNAc1,4GlcNAc (LDN) structure [78, 79]. The study employed highly efficient techniques such as recombinant WFA and plasmon field-enhanced fluorescence spectroscopy immunosorbent systems, which proved to be 100 times more sensitive than conventional Elisa techniques and can thus be used clinically for the serodiagnosis of early-stage CCC, which is challenging to detect using currently available serum markers [79].

Other Important Lectins and Cancer Diagnosis

HCC and benign liver disease may be distinguished by erythrocyte-agglutinating *Phaseolus vulgaris* agglutinin [63]. Furthermore, *Sambucus nigra* agglutinin may be employed to identify cancer-associated sialyl Tn-antigen in the blood and cancer-associated sialylated glycoproteins in the blood at extremely low levels [78, 80]. Peptide nucleic acid (PNA 1) [81, 82] might aid in the identification of the Thomsen–Friedenreich antigen, a galactosyl-(1, 3)-N acetyl-D galactosamine molecule seen in colorectal cancer and other malignancies. More study is needed to understand the non-invasive development of cancer tissue and/or cancer cell-specific reactivates to the lectins described above.

Current Lectin Applications in Cancer Detection and Therapy

Because of their outstanding glycan recognition property, they have a wide range of applications in analytical biochemistry, biotechnology, and surface chemistry. Furthermore, because of its stability, novel drug delivery approaches seek to employ lectin for drug administration, reducing undesirable toxicity. Non-specific binding interactions are being created, as are methods for regulating them. Lectins have the potential to be employed in nanotechnology to target and image cancer. Many investigations in the field of lectinology are being conducted to uncover breakthroughs with therapeutic translation potential. As a consequence, lectins may be able to identify such changes, making them useful in cancer diagnosis and treatment. Further research on effective drug delivery system procedures for lectins is necessary to properly use these proteins [83]. Recent breakthroughs in lectin research have focussed on the use of plant lectins in the identification and treatment of human cancer [84].

Clinical Translation of Anticancer Lectins

Plant lectins have indeed been detected in cells and animals as harmful substances for decades, but a new study suggests that they may have an inhibitory effect on cancer growth. Due to the cytotoxic, apoptotic, and autophagic actions of plant lectins and because dietary lectins may be intact, the use of plant lectins in combating cancer is presently transitioning from detection to actual cancer [85]. In post-surgical post-preservation patients with primary intermediate to high-risk malignant melanoma (UICC/AJCC phase II–III), a standardised European mistletoe (*V. album* L.) extract from Iscador fermented mistletoe extract (FME) was compared to an untreated control group for safety and effectiveness. Long-term FME therapy is safe without the requirement for further tumour augmentation. When differentiated to the untreated control group of persons at cancer stages II–III, there was also a substantial survival benefit [86].

Another study found that mistletoe manufactured with 10.000 ng/ml injectable ampoules had a survival benefit of 2–5 months for people in a variety of scenarios with low toxicity and anti-tumour effects. The profile of patients who have mistletoe has been found in clinical investigations. Further research on the survival rate of additional active drugs, tumour remission, the quality of life linked with cytoreductive therapy side effects is warranted [87]. The safety profile of the recombinant component of natural mistletoe lectin-1, aviscumine, in terms of dose-limiting toxicities (DLT) and maximum dosage for cancer patients in clinical situations was also investigated.

Advanced Lectins Formulations for Cancer Theranostics

Gold nanoparticles (AuNPs) are widely employed in bioimaging and phototherapy at the moment. Because of their distinctive optical qualities, they can be employed in whole-body scans to aid in cancer diagnosis. Recently. AuNPs of various sizes and shapes have been created, and their production is based on 18 synthetic processes. They might be used as a cancer detection NIR-active imaging probe. Plasmon resonances can be employed to boost the optical response as well [88]. The number of AuNP-PEGylated GNRS employed in cancer imaging was much higher than the number of non-targeted PGNRs. These findings suggest that CET-pGNRS can target tumours precisely and is effective for cancer detection [89, 90].

Au nanoparticles (AuNPs) were prepared, and their surfaces were modified with a carbohydrate, which has the binding capability to a plant lectin. We can create polyp-targeting fluorescently tagged AuNPs that can be used as endoscopic contrast agents to detect tumour cells early. This research implies that lectin-functionalised fluorescent AuNPs might be a suitable endoscopic contrast agent for premalignant tumour cell in situ diagnostic imaging [91].

Challenges, Future Prospect, and Research Direction for Novelty and Advancement of the Research Field

The major concern about lectin dosage is that it may be very toxic in nature, which sometimes leads to death or organ failure. With this dynamic glycan recognition molecule, targeted cancer treatment is a great task, but a hindrance is its toxicity. Studies on trials of Con A lectins on mouse intravenous injections showed liver failure. Oral treatment of the phytohaemagglutinin (PHA) lectins causes vomiting and diarrhoea. Abrin and ricin are also known toxic lectins in mice. There are two ways in which scientists can overcome this issue: by identifying non-toxic lectins that can be used in cancer treatment, diagnosis, and removal of the toxicity of the lectins by different methods. The solutions for the toxicity extenuation of the lectins were made by fusion of the toxic domain of the lectins with proteins for targeted delivery to the malignant cells.

The lack of promising markers for early cancer diagnosis and effective treatment is the reason why deaths due to cancer are higher globally. Lectin is widely distributed in nature and has multiple applications, right from defence to cancer recognition and diagnosis. The present review focussed on plant-origin lectins, which are available easily in nature and can be effectively utilised for early cancer diagnosis and treatment as an alternative to the available tools in the same application. The use of plant-based formulations for cancer theranostics is an emerging field in the early diagnosis and treatment of cancer. The available information on plant-based lectins in clinical aspects can be further explored for their properties, mechanisms of action, and how effectively they can be used in cancer therapeutics while reducing possible pessimistic effects. These are some niches that need to be addressed through systematic research, experiments, and studies.

Conclusion

The application of lectins for cancer detection, imaging, and therapy has attracted researcher's interest. Although the clinical interpretation of these data remains a major impediment, the science of lectinology will expand in the upcoming years. Future research will focus on developing safe and effective lectin delivery systems to optimise therapeutic efficacy and raise the chance of clinical translation. Indeed, lectin-induced inflammation, poisoning, and enzyme resistance are only a few of the reasons why these powerful proteins are being avoided. Although lectin molecules have a promising future in cancer detection and therapy, future research should focus on reducing their negative effects (cytotoxic and immunomodulatory, for example) and improving the effective use of lectin in medicine through thorough in vitro and in vivo investigations. The lectin formulation for cancer theranostics, on the other hand, is a new field in cancer early diagnosis and therapy.

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Declarations

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