Types of lectins and their therapeutic potential

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ABSTRACT:

The survival of any cell or an organism depends on its immune system activity. This immune system activity depends on the organism's interaction with the environment. Eventually any organism (from prokaryotic to eukaryotic) depends on a certain set of proteins present on the cell surface, as these cell surface proteins, named Lectins, primarily interact with cells of other organisms. There are various lectins known to occur in plants and animals (vertebrates and invertebrates). Moreover, every lectin is known to have specific binding with the surface glycoproteins of other cells. This eventually leads to a myriad of reactions leading to their therapeutic usage as antibacterial, antiviral & anticancerous agents in the medical field. The review focuses on the various lectins studied till date and their therapeutic potential.

KEYWORDS: Lectin, Glycoprotein, Antibacterial, Anticancerous, Antiviral.

INTRODUCTION:

The survival of any cell or an organism depends on functioning of its immune system activity. This immune system activity depends on the interaction with the environment. Eventually any organism (from prokaryotic to eukaryotic) depends on a certain set of proteins present on the cell surface, as these cell surface proteins primarily interact with cells of other organisms (Nicholson, L. B. 2016, Salvador et.al. 2021). For example, cell receptors communicate with a ligand or protein from the neighbouring cell or environment and begin a downstream pathway. The downstream pathway leads to a cascade of signalling proteins which either trigger or inhibit gene regulation (Torii, K. U. 2004). Similarly, there exists a protein group named 'Lectin' that performs a similar activity. Lectin is responsible for cellular recognition using carbohydrate moieties (CM) (Hassan et.al. 2020).

Lectin uses different carbohydrate moieties to differentiate between self and non-self cell types. This phenomenon is used in immunity, reproduction and various other cellular functions (Das et.al. 2022). For example, a plant is able to differentiate between the pollen of a similar species and other species, depending on the CM present on the cell surface (Hafidh, S., Fíla, J., & Honys, D. 2016), (De Coninck, T., & Van Damme, E. J. 2021).This property is employed in developing therapeutics against diseases such as cancer, microbial infection, cardiac disorders and others.

Lectins exist naturally on cell surface of a myriad of plants, animals and microbes. (Naeem et.al. 2007). Each lectin has specific structure & function (Pusztai et.al. 2008), (Soltanian et.al. 2009).

Lectins are cell-surface glycoprotein-binding proteins. But their binding affinity is highly specific and forms weak as well as strong interactions, leading to agglutination.

Types of cell surface glycoproteins for binding of lectin:

There are various types of surface glycoproteins such as N-Acetylglucosamine, mannose, fucose, N-Acetylgalactosamine and N-acetylneuraminic acid. Out of these N-Acetylglucosamine, mannose, and fucose belong to O-linked glycan category while N-Acetylgalactosamine belongs to N-linked glycans group of glycoproteins (Šimonová et.al. 2021). Lectins are implicated to have specific roles and binding affinity with other cell surface glycoproteins (Dias et.al. 2015). Eventually, this property confers cellular aggregation and reactivity; leading to numerous therapeutic applications in the medical field (Chettri et.al. 2021).

1. Mannose binding lectins

A.Concanavalin A (ConA):

Concanavalin A (ConA) is a D-mannose specific binding lectin that is formed of ~290 amino acids (Derewenda *et.al.*1989) (Heymann et.al. 2015). This glycoprotein weighs around 31.48 kDa and binds to manganese or calcium ions. These ions are vital for cell-agglutinating and saccharide binding activity. Also, ConA is known to confer antiviral properties and contribute towards defence against numerous bacterial infections, thus used as therapeutics in various diseases. (Marchetti et. al., 1995)

An antibiotic consisting of ConA-coated mesoporous silica nanoparticles was developed in 2019 to assess antimicrobial activity. This technique yielded an increase in anti-microbial activity against a culture of *Escherichia coli*. Along with this, these nanoparticles exhibited biocompatibility with the mouse cell line 'osteoblastic MC3T3-E1'. This application is suitable for treating infections; as these particles showed absence of cytotoxicity and lacked immunogenicity (Martínez-Carmona et.al. 2019).

The antioxidant and hepatoprotective roles of ConA-induced liver damage against Chitosan-Stabilised Selenium Nanoparticles was assessed in mice model by Bai and group in 2020. Their findings suggest that selenium nanoparticles sized ~60 nm particles exhibit radical scavenging potentials against 2,2-diphenyl-1-picrylhydrazyl, hydroxyl ions and superoxide anions. Moreover, the results obtained were a result of lipid retardation, lipid oxidation and by upregulating catalase, glutathione as well as superoxide dismutase activity in the affected mice cells. The antioxidant treatment of mice was facilitated by providing selenium nanoparticles in powder form. This resulted in maintaining glutathione levels and upregulating catalase, glutathione peroxidase and superoxide dismutase levels in mice models (Bai *et.al.* 2020). To summarise, their findings provide conclusive proof of using a combination of Selenium nanoparticles and ConA as a therapeutic against oxidation triggering diseases such as cancer.

Huldani and colleagues in 2022 noticed autophagic and apoptotic effects of ConA in different types of cancer cells (HeLa, Bone marrow-derived dendritic cells, U87 glioblastoma, MDA-MB-231, MCF-7 and others), P73 and JAK/STAT3.Hence, ConA can be regarded as a potential anticancer drug for clinical trials (Huldani et.al. 2022).

B.Snowdrop lectin:

Snowdrop lectin (GNA), a D-linked mannose-specific lectin consisting of ~157 amino acids, was first extracted from *Galanthus nivalis*, hence the abbreviation GNA (*Galanthus nivalis* agglutinin). GNA has a mass of around 16 kDa and displays a high affinity for α-(1-3)-mannose oligomers. These glycoproteins display

antiviral and insecticidal properties. (Balzarini et. al., 1991)

In 2014, Nakasu and team combined a spider venom with GNA to assess insecticidal properties against *Myzus persicae* (peach-potato aphids) & found 40% reduction in the survival of the aphids as they fed on *Arabidopsis thaliana* leaf. *Sitobion avenae* (Grain Aphids) were more susceptible to *Myzus persicae* as they were unable to hydrolyse the spider venom and GNA fusion protein in their system. In conclusion, certain host plants will be able to demonstrate a high degree of resistance towards *M. persicae* when they possess the spider venom with GNA fusion protein (Nakasu et.al. 2014).

.Furthermore, a study based on the use of a recombinant protein ω-ACTX-Hv1a (spider venom) and GNA as an insecticide on *Myzus persicae* (Peach-potato aphid). The recombinant protein construct was found predominantly in the *Arabidopsis thaliana* leaf; as the construct was easily degraded in the plant body. The study indicated a 40% increase in the mortality rate. This finding can further be used to assess the toxicity and efficacy in other plants as well. As this would eventually boost crop yield in the agricultural sector (Nakasu et.al. 2014).

C. Lentil lectin (LCH):

Lentil lectins are mainly found in *Lens culinaris* that are composed of 275 amino acids and a molecular mass of ~30kDa. This D-mannose specific binding lectin comprises two manganese and two calcium metal ions; also these ions are essentials for saccharide binding activity only (Deeksha et.al. 2021).

In the study, on 12 plant derived lectins for anti-SARS-CoV-2 activity, *Lens culinaris*-derived lectin was able to bind with mannose and N-Acetylglucosamine and exhibited antiviral activity against MERS-CoV and SARS-CoV-2 & was also able to inhibit Angiotensin-converting enzyme 2 receptor; thereby blocking SARS-CoV-2 activity (Wang et.al. 2021).

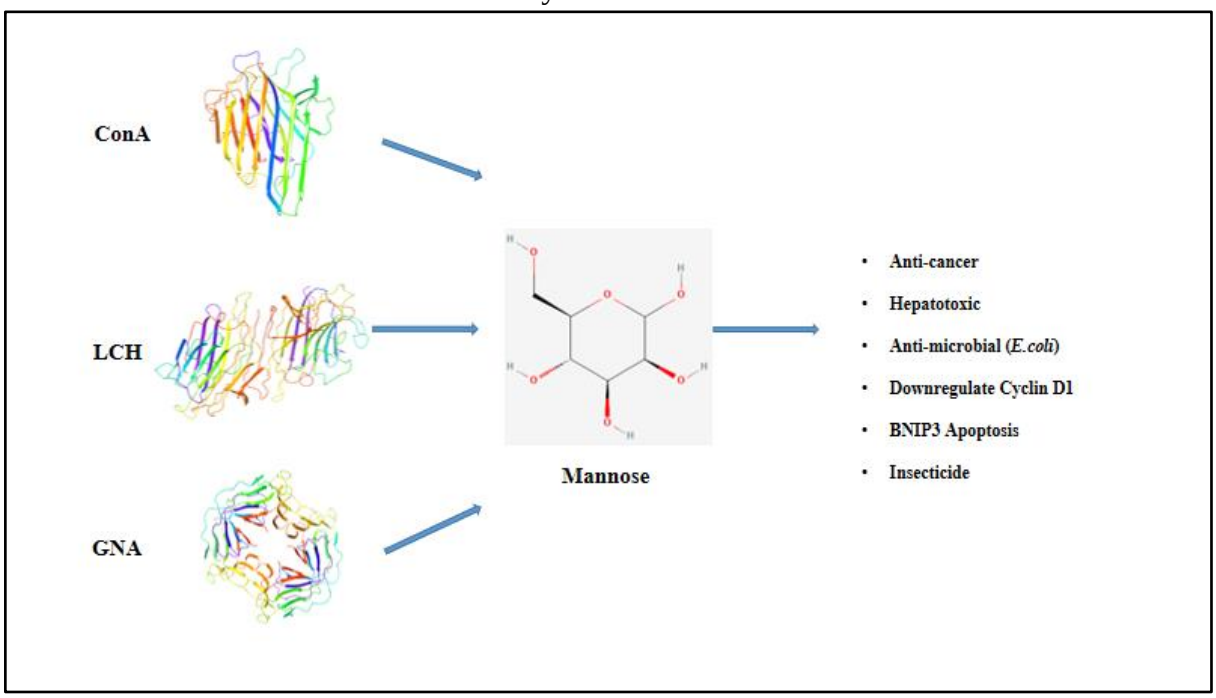

Figure 1: Overview of Mannose binding lectins ConA (Concanavalin A), LCH (Lentil lectin) and GNA (Snowdrop) and their therapeutic effects.

2. Galactose/ N-acetylgalactosamine binding lectins

A. Jacalin (AIL)

Jacalin (JCA) is a D-galactose specific binding lectin, mostly found in Jackfruit (*Artocarpus heterophyllus*), has a molecular mass of ~14kDa and is formed of around 133 amino acids. It is a potent stimulant of B and T lymphocytes according to various studies (Jain et.al. 2022).

In 2019, study by Jung and colleagues focused on the role of rice mannose-binding jacalin-related lectin (OsJAC1) in rescuing DNA damage caused by gamma radiation in Rice seeds. The OsJAC1-overexpressing Arabidopsis lines were used to test the implications of gamma radiation. They found that OsJAC1-overexpression was a crucial player in rescuing damaged DNA in Rice seeds. Also, they observed expression changes in certain genes such as ATM, MCMs, MRE11 and RPA. As these genes are a part of perception regulatory components in plant cells (Jung et.al. 2019).

These new findings could be further applied in the agricultural sectors to enhance crop production and reduce crop damage.

An in vitro study based on the antibacterial effects of copper sulphide nanoparticles combined with Jacalin was conducted in 2018 against *Aeromonas hydrophila*, *Bacillus subtilis*, *E. coli* and *Staphylococcus aureusmulti* multidrug resistant strains indicated increase cell death in these bacterial strains. A study on novel antibacterial ability in *Danio rerio* infected by *Aeromonas hydrophila* was thoroughly conducted in 2018 by Ahmed and colleagues. The study was based on developing a non-toxic drug that had a platinum salt (not antibacterial) and Jacalin (non-immunogenic). They used Jacalin-capped platinum nanoparticles to confer protection against *A.hydrophila.* The treatment was also able to trigger adaptive immunity responses in *Danio rerio*; so they were able to survive for 21 days post treatment (Ahmed et.al. 2018). This method could also be used to test the antibacterial ability against other pathogenic bacterial strains.

In a recent study, researchers found that Jacalin was able to induce macrophage mediated proinflammatory cytokines antitumor activity. Also & the cytokines were released via the NF-κB signalling pathway. This led to apoptosis in the human colon and breast cell lines (HT-29 and MCF-7 respectively) (Polli et.al. 2016). Overall additional studies are required to assess the antitumor and anticancer potentials in other cancer cell lines as well. This could pave a new way for Jacalin as anticancer therapeutics.

B. PNA (Peanut agglutinin):

PNA or Peanut agglutinin is a D-galactose binding specific lectin found prominently in peanuts (*Arachis hypogaea*). This 29 kDa protein binds with a manganese and calcium ion. These ions are crucial for cell-agglutinating and saccharide binding based activities (Belardin et.al. 2019). Selenium effectiveness was assessed by using different lectins on chondrocyte glycoprotein; as the pathogenesis of Kashin-Beck Disease (disabling osteoarthropathy) relies on this. The study involved culturing chondrocytes with and without selenium to assess the lectin levels

in both samples. Moreover, a Lectin microarray was used for the analysis. The results yielded strong binding affinity for *Bandeiraea simplicifolia* (BS-I), *Hippeastrum hybrid* lectin (HHL), Lotus *tetragonolobus lectin* (LTL), *Pisum sativum* agglutinin (PSA), *Psophocarpus tetragonolobus* lectin I (PTL-I), *Psophocarpus tetragonolobus* lectin II (PTL-II), *Sophora japonica* agglutinin (SJA), , and *Triticum vulgaris* (WGA) against chondrocytes without selenium culture. However, signals were weaker for *Aleuria aurantia* lectin (AAL), *Lens culinaris* agglutinin (LCA), *Lycopersicon esculentum* (tomato) lectin (LEL), Peanut agglutinin (PNA), and *Sambucus nigra* lectin (SNA). The study also concluded that selenium might influence the expression levels of galactose, mannose and N-Acetylglucosamine in the culture samples (Wang et.al. 2022). Therefore the study points towards the efficient use of lectins in detecting the extent of pathogenesis in Kashin-Beck Disease.

Rangel and colleagues developed an impedimetric biosensor using peanut agglutinin derived from *Arachis hypogaea* to detect cancer associated T-antigens. Using this method, the peanut agglutinin was able to recognise and bind to T-antigen glycoproteins. The same method was used to detect Asialofetuin (a glycoprotein extracted from foetal calf serum). The Asialofetuin was employed as positive control in this experiment and yielded an increase in impedance by 7.2%. The T-antigens of different cancer serum samples such as breast, colon, lung, kidney, prostrate, skin, stomach and rectum were analysed using the impedimetric biosensor. Also, the study concluded that peanut agglutinin was more efficient in cancer T-antigen detection. Thereby, a combination of different lectins for impedance can be used for cancer T-antigen detection (Rangel, M. G., & Silva, M. L. S. 2019).

C.Ricin (RCA):

Ricin, derived from castor (Ricinus communis) seeds, is a N-acetylgalactosamine binding lectin consisting of 576 amino acids & comprises of two peptide chains; of these the B chain binds with β-D-galactopyranoside of the glycoproteins on the cell surface (Yu et.al. 2022).

Activity of Ricin-B-lectins with respect to antifungal potential was ascertained in a study by using *Leptinotarsa decemlineata* (Colorado potato beetle). The fungal cultures *Beauveria bassiana* and *Metarhizium robertsii* were used for this analysis against Ricin-B-Lectin. The study indicated marked increase in fat depositions of *Leptinotarsa decemlineata* upon fungal infections from both strains. Further, there was an upregulation in the LdRBLk (*Leptinotarsa decemlineata* Ricin-B-lectin-k) gene in response to thermal stress on the Colorado potato beetle. This gene upregulation was in correlation with *attacin* (antibacterial peptide); but was unable to be correlated with *hsp90* gene. Therefore, the study suggests the viability of Ricin-B-Lectin as an antifungal therapeutic against *Beauveria bassiana* and *Metarhizium robertsii* strains (Rotskaya et.al. 2021). The study prompts research towards the assessment of Ricin-B-Lectin on pathogenic fungal species in the future.

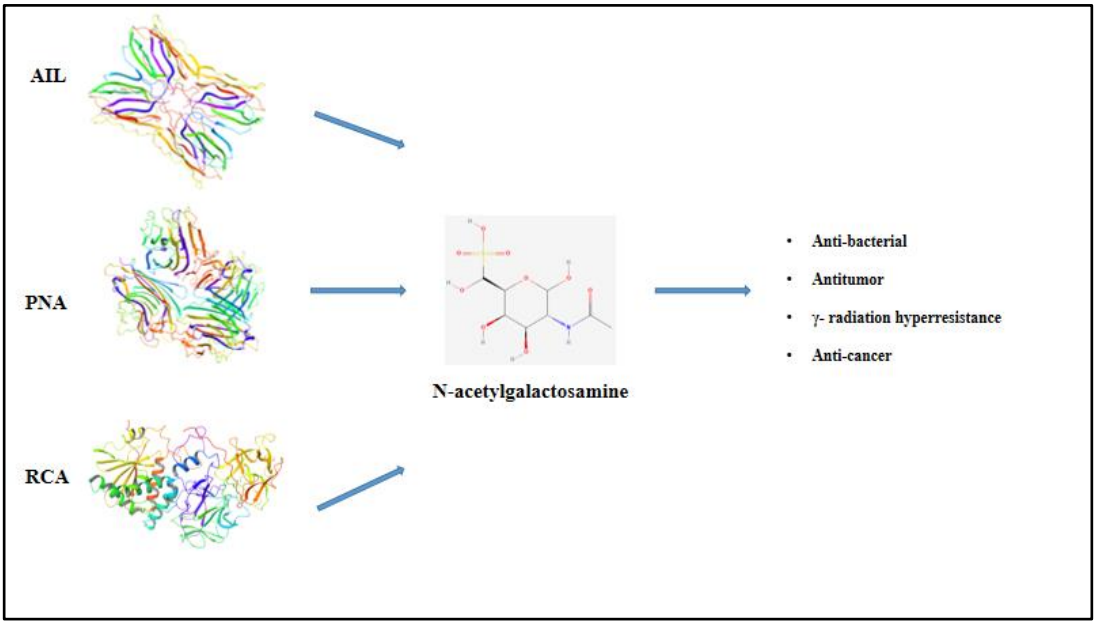

Figure 2: Overview of N-acetylgalactosamine binding lectins AIL (Jacalin), PNA (Peanut agglutinin) and RCA (Ricin) along with their therapeutic effects.

3. N- acetylglucosamine binding lectins

A. Wheat germ agglutinin (WGA):

Wheat germ agglutinin (WGA) is a N-acetylglucosamine binding lectin composed of 171 amino acids with a mass of WGA is around 18kDa. (Jain et.al. 2022).

A lectin/agglutinin interaction-based study was conducted to assess the contribution in autoimmune disorders. They observed that WGA was highly reactive lectin as compared to kidney bean/phytohemagglutinin, soybean agglutinin and peanut agglutinin. In conclusion, they deduced that the undigested lectins might be a possible source for triggering autoimmune disorders in humans (Vojdani et.al. 2020).

An anticancer drug delivery system was developed by Kuo and colleagues in 2019 by combining wheat germ agglutinin and folic acid along with methoxy poly (ethylene glycol) (MPEG)-poly(ε-caprolactone) (PCL) nanoparticles to treat glioblastoma. They successfully stabilised these nanoparticles using a microemulsion-solvent evaporation technique. Additionally these nanoparticles were loaded with anticarcinogenic drugs like carmustine, doxorubicin and etoposide to assess their binding affinities. Their findings revealed anti-inflammatory properties of WGA and folic acid loaded nanoparticles to have the highest binding affinity as compared to only folic acid or wheat germ agglutinin treated samples. On the other hand, the wheat germ agglutinin and folic acid nanoparticles combined with carmustine, doxorubicin and etoposide demonstrated nanocarrier properties against glioblastoma cells (Kuo et.al. 2019).

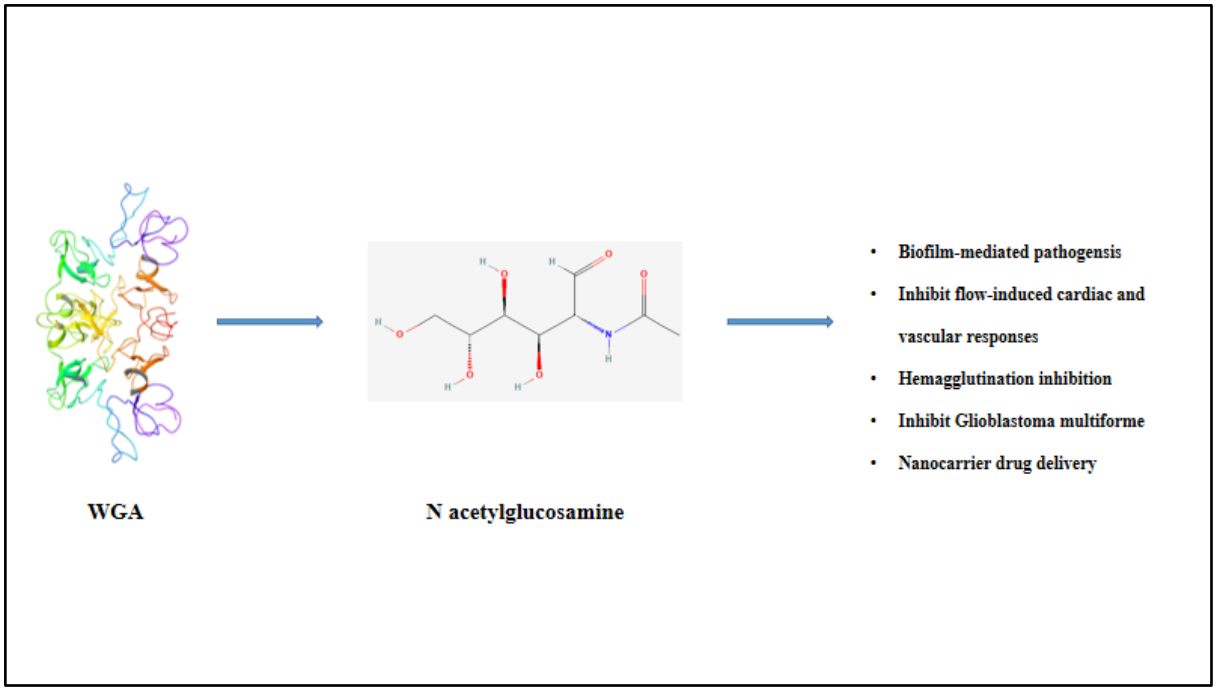

Figure 3: N-acetylglucosamine binding lectin WGA (Wheat germ agglutinin) and the corresponding therapeutic effects.

4. N-acetylneuraminic acid binding lectins

A. Elderberry lectin (SNA):

Elderberry lectin is the most versatile studied protein in glycobiology. This protein is mainly composed of 570 amino acids and has a molecular mass of 26-240 kDa; binding to N-acetylneuraminic acid. This is the second largest lectin and is known to inhibit mammalian ribosomes. Additionally, this lectin is mainly studied as an insecticide (Tejero et.al. 2015). Recent Elderberry lectin-related research and studies have been reviewed and summarised as follows.

The sensitivity of elderberry lectins to proteolysis triggered by duodenal as well as gastric fluids was analysed In vitro. The elderberry bark is known to contain type II ribosome-inactivating proteins (RIP). These Type-II RIP's were found to be sensitised towards hydrolytic enzymes upon boiling in a water bath for 10 minutes. Post water bath incubation, it was found that the antioxidant, anthocyanins, cyanidin-3-glucoside, cyanidin-3-sambubioside, free-radical scavenging activities and Folin-Ciocalteau's reagent reactive compounds were unaffected. In short, this treatment is useful in diminishing the allergic reactions triggered due to consumption of elderberry (Jiménez et.al. 2017).

Recently during the COVID-19 pandemic, it was found that the major clinical feature was a microvascular thrombosis that was linked to endothelial cell activation of coronavirus. In addition, patients with severe COVID-19 infection had elevated von Willebrand Factor (vWF) levels in the plasma. This von Willebrand Factor mainly contributes to the thrombotic phenotype in COVID-19 patients. In this regard, the sialic acid levels were measured using Elderberry bark lectins as these lectins showed specific binding with vWF In vitro. The work concluded that the vWF levels and sialic acid were inversely proportional.

In short, patients with low sialic acid levels and high vWF levels were severely affected by COVID-19 disease (Mobayen et.al. 2021).

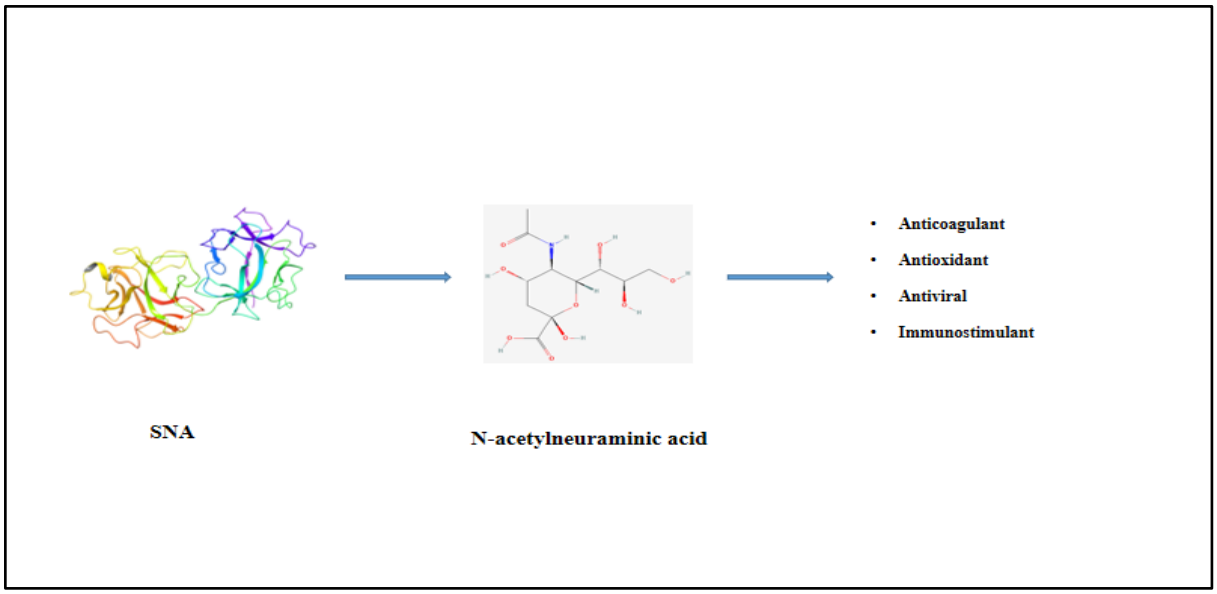

Figure 4: SNA (Elderberry lectin) binding with N-acetylneuraminic acid demonstrating remedial activities.

5. Fucose binding lectins

A. *Aleuria aurantia* lectin (AAL):

An L-Fucose binding lectin abbreviated AAL is composed mainly of 313 amino acids and has a mass of ~72kDa. AAL is a known antifungal (against *Mucor racemosus*) and anticancer (against liver cancer) agent. Along with this, *Aleuria aurantia* lectin plays a crucial role in fruiting body differentiation in plants (Kekki et.al. 2017). This section reviews and discusses the most recent updates in studies conducted on AAL.

The use of AAL for detecting and monitoring cancer specific antigens was conducted in 2017 by Kekki and colleagues. They analysed different cancer samples such as recombinant precursor PSA, serum prostate-specific antigen and seminal plasma prostate-specific antigen for difference in the fucosylation levels. Novel lectin immunoassay was utilised, as this method uses PSA-Fab fragments or europium-labelled AAL or AAL-europium coupled with chelated dye nanoparticles to detect fucosylation on the PSA. They found higher levels of fucosylation of PSA in seminal plasma PSA as compared to urine and benign tissue samples. Also, the AAL-europium coupled with chelated dye nanoparticles increased the overall sensitivity of the lectin immunoassay for detecting fucosylation in cancer samples (Kekki et.al. 2017). This method might serve as an early detection and monitoring technique for various cancer samples in the near future.

The pentavalent binding of AAL with human derived human liver cancer serum was assessed in 2016. They observed that AAL was able to bind with fucose at α-1,2, α-1,3, α-1,4 and α-1,6. In addition, the lectin mutant N224Q was also characterised in this study. They found that the fetal cell lines produced several surface glycoproteins bound to N224Q lectins. Therefore, AAL is a potential candidate for

detecting hepatocarcinoma cell lines in further studies (Norton et.al. 2016).

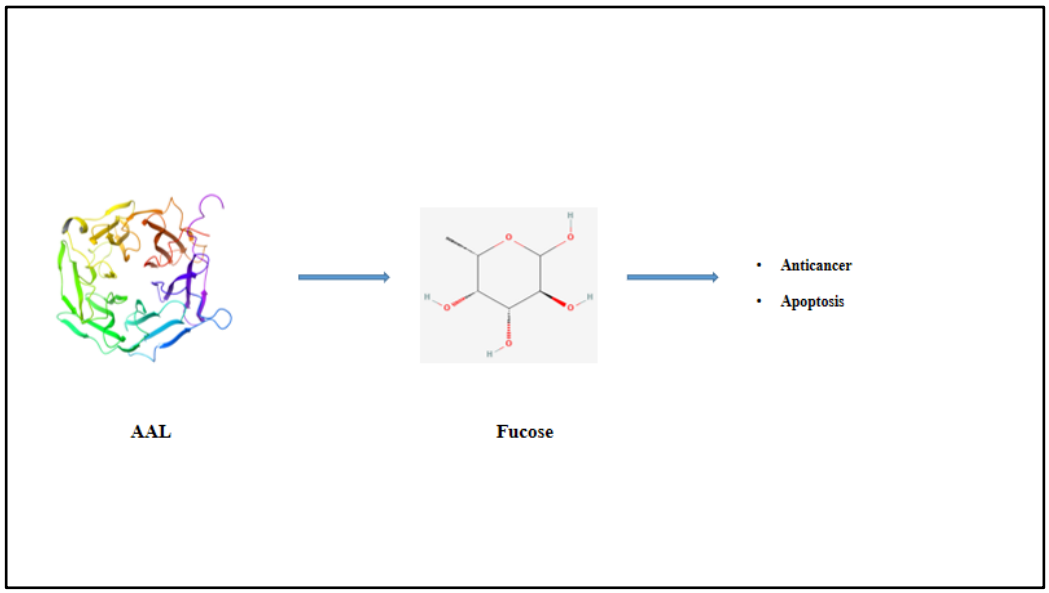

Figure 5: AAL (*Aleuria aurantia* lectin) binds with Fucose to confer Anticancer and Apoptosis.

CONCLUSION:

Various types of lectins described in this review point towards the therapeutic properties and potentials in various diseases. Jacalin, Elderberry lectin and peanut agglutinin are the most versatile and efficient lectins till date. Moreover, these lectins are highly efficient in detection, monitoring and are viable candidates as therapeutics in the near future. Although a thorough investigation on the compatibility of these proteins could be carried out using different computational biological techniques to assess their undiscovered therapeutic potentials. This would eventually aid in the novel drug designing and drug delivery of lectins.

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