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Roles of Plant and Fungal Lectins in Cancer Diagnosis and Treatment: A Scoping Review

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Abstract

Lectins are proteins that possess the carbohydrate-binding property that makes the lectins can bind and recognize carbohydrate moieties on cancer cells. Lectins trigger various cell death forms such as apoptosis, autophagy, and necrosis in various cancer cell lines. These abilities of lectins are making the lectins a potential and convenient tool for cancer treatment and diagnosis. According to carbohydrate specificities and affinities, sequence similarities, the number of carbohydrate-binding domains, etc., lectins are classified into many groups. Therefore, the different lectins in each other have distinct affinities in various cancer cell lines. The researches and reviews of the potential use in cancer treatment and diagnosis of plant and fungal lectins have been aimed to document in this review.

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Highlights

This scoping review summarizes the researches and reviews regards to the potential use of lectins in cancer diagnosis and treatment, and also brings together the main findings of cancer studies with lectins, allowing for clarification of studies on this subject and identifying gaps in the literature.

Kanser Tanısında ve Tedavisinde Bitki ve Mantar Lektinlerinin Rolü: Derleme

Özet

Lektinler, kanser hücrelerindeki karbonhidrat parçalarına bağlanabilmelerini ve tanımalarını sağlayan karbonhidrat bağlama özelliğine sahip proteinlerdir. Lektinler, çeşitli kanser hücre dizilerinde apoptozis, otofaji ve nekroz gibi çeşitli hücre ölüm şekillerini tetikler. Lektinlerin bu yetenekleri, lektinleri kanser tedavisi ve teşhisi için potansiyel ve uygun bir araç haline getirmektedir. Karbonhidrat spesifiteleri ve afiniteleri, dizi benzerlikleri, karbonhidrat bağlama alanlarının sayısı ve benzerine göre lektinler birçok gruba ayrılır. Bu nedenle, birbirinden farklı lektinler, çeşitli kanser hücre dizilerinde farklı afinitelere sahiptir. Bu derlemede, bitki ve mantar lektinlerinin kanser tedavisi ve teşhisinde potansiyel kullanımı ile ilgili araştırma ve incelemelerin belgelenmesi amaçlanmıştır.

Anahtar Kelimeler

Lektin, Kanser, Apoptozis, Otofaji, Risin, Concanavalin A

Öne Çıkanlar

Bu derleme, kanser teşhisi ve tedavisinde lektinlerin potansiyel kullanımlarıyla ilgili araştırılmaları ve incelemeleri özetler ve ayrıca kanser çalışmalarının ana bulgularını lektinlerle bir araya getirerek bu konudaki çalışmaların netleşmesine ve literatürdeki boşlukların belirlenmesine olanak tanır.

1. LECTINS, THEIR PROPERTIES, AND CLASSIFICATIONS

Lectins, present in various organisms such as plants, animals, and bacteria, and are non-immune originated proteins that contain at least one non-catalytic domain that makes the lectins able to reversibly bind and selectively recognize glycans and carbohydrates without altering their structures [1-6]. The non-catalytic domain is called Carbohydrate-Binding Domain (CBD) and is located in a specific polypeptide segment [7,8]. Lectins interact with carbohydrates through a hydrogen bond, hydrophobic interactions as well as van der Waals interactions, and metal ions can play a role in the interactions of some lectins [8-12]. Any modifications that occur in the CBD can cause an alteration in the binding property and biological functions of the lectins. For example, *Polygonatum cyrtonema* Hua. lectin (PCL) has three CBDs called CBDI, CBDII, and CBDIII. CBDI is capable to bind to mannose, but in CBDII, the modification which is replaced the Gln58 and Asp60 with His58 and Asn60 respectively makes the CBDII incapable to bind to mannose [11,12].

Besides lectins have been known to play a role in many biological processes such as metastasis, regulation of intracellular traffic, intracellular protein transportation, exocytosis, endocytosis, cell adhesion, cell-cell communications, differentiation of the cells, stimulation of the macrophages, body defense, attachments of infectious agents to target cells, the guidance of the leukocytes to inflammation, their first recognition is due to their ability to agglutinate erythrocytes [4,8,10,13-20]. Additionally, plant lectins take part in preventing the plants from insects and funguses, and also have a role in

carbohydrate transportation and storage [12,21]. Because the lectins cause no alteration on the structures of carbohydrates, they differ from the enzymes [8,10].

Lectins are classified in many different groups due to their properties such as the sources from that they are extracted, carbohydrate specificities and sequence similarity. According to the properties of binding to the monosaccharides; *1- Galactose specific, 2- Mannose or glucose that present on the N-linked oligosaccharides, 3- L-fucose specific, 4- N-acetylglucosamine (GlcNAc) specific, 5- N-acetylgalactosamine (GalNAc), and 6- Sialic acid specific* [8,22]. According to carbohydrate-binding properties; *1- Agaricus bisporus agglutinins, 2- Amaranthins, 3- Class V chitinase homologs with lectin activity, 4- Cyanovirins, 5- Euonymus europaeus (EEA) agglutinins, 6- Galanthus nivalis (GNA) agglutinins, 7- Heveins, 8- Jacalin lectins, 9- Legume lectins, 10- LysM lectins, 11- Nictaba lectins,* and *12- Ricin-B lectins* [12,23]. Plant-derived lectins are classified into four groups according to their structure and the number of carbohydrate-binding domains; *1- Merolectins, 2- Hololectins, 3- Superlectins,* and *4- Chimerolectins.* Merolectins have a single CBD and cannot agglutinate the erythrocytes. Unlike the merolectins, hololectins have at least two similar CBD and many of them can agglutinate erythrocytes. Superlectins can bind to different carbohydrates because they have CBDs with distinct binding properties. Additionally, chimerolectins have a single or more CBD and an unrelated protein that has catalytic activity independent from the CBDs [24]. Although the fungal lectins have been classified into the same groups as animal and plant-derived lectins because of the sequence similarity, sequences of some fungal lectins are dissimilar to animal and plant-derived lectins. Therefore, these lectins that have divergent sequence are classified into three groups; *1- "Fungal Fruiting Bodies" Agaricus bisporus lectin-like family, 2- Fucose specific Aleuria aurantia lectin-like family,* and *3- Pholiota squarrosa lectin-like family* [25].

2. Apoptosis

Apoptosis is a cell death form that is tightly regulated, and characterized by membrane blebbing and apoptotic bodies, and also is triggered during the development of an organism or under pathological conditions. The formation of the apoptotic bodies blocks the release of the cellular content to the out of the cell, thus inflammatory responses that might occur after the release of the cellular content are avoided. Subsequently, these apoptotic bodies must be phagocytized quickly, so, macrophages, parenchymal cells, and neoplastic cells take part in this process. Unlike necrosis, phosphatidylserine is translocated to outwards of the cell during apoptosis to mark the cell for macrophages or other phagocytic cells. Apoptosis can be initiated by different pathways. There are two major apoptosis initiator pathways which are the extrinsic pathway and the intrinsic pathway which is called the mitochondrial-dependent pathway. Additionally, there is another pathway that can trigger apoptosis, the perforin-granzyme pathway [26].

In the extrinsic pathway, the interaction between death receptors that belong to the tumor necrosis factor (TNF) receptor family and their ligands which are called death ligands induce apoptosis [26].

The intrinsic pathway can be initiated by various stimulations. These stimulations cause the release of pro-apoptotic proteins such as cytochrome c, and trigger apoptosis by causing the loss of mitochondrial membrane potential [26]. The mitochondrial membrane potential is regulated by anti-apoptotic proteins such as Bcl-2, Bcl-XL, and Mcl-1 and pro-apoptotic proteins such as Bax and Bak [4,27,28].

In the transformed or infected cells, the perforin-granzyme pathway can initiate apoptosis through the perforin that forms pores on the cells to facilitate the entrance of the serine proteases which are called granzyme A and granzyme B to the target cell. The perforin is released by cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells [26].

Finally, the execution pathway is triggered by caspase activity. In this pathway, initiator caspases such as caspase-8, caspase-9, caspase-10 can activate directly caspase-3 which is an execution caspase, to activate cytoplasmic endonucleases to degrade nucleus material, and the proteases to degrade the nuclear and cytoskeletal proteins [26].

3. Autophagy

Autophagy is a cell death type that is a degradation process of damaged macromolecules or organelles by lysosomal hydrolytic enzymes, and which can be inhibited by high glucose, Akt, mTOR, or PI3K signal pathway. Also, autophagy is related to cell survival, and controls the quality of proteins and organelles. There are three major autophagy pathways, macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [29].

In macroautophagy, double membraned autophagosomes form from the elongation of a *de novo* isolation membrane which is regulated by various proteins to degrade the cytosol content in the lysosome [29-31].

Microautophagy is the second major pathway of autophagy that is the soluble and particle-sized cell contents are taken directly to the lysosome, and it is regulated by TOR and EGO signaling complexes [29,32].

Chaperone-mediated autophagy is a degradation process of only soluble proteins in highly organized eukaryotes, which is also no need for to formation of a vesicle [29,31]. Lysosome-associated membrane protein 2A (LAMP2A), a translocation protein complex that facilitates the entrance of the substrate to the lysosome and chaperone proteins get involved in this type of autophagy [29]. Notably, the protein must possess a KFERQ amino acid sequence to be a substrate of CMA [29,33].

4. Necrosis

Necrosis is a cell death form that is unprogrammed and passive and is observed randomized DNA fragmentation [26,34]. Unlike apoptosis, inflammatory responses occur in necrosis. Also, there is no need for the energy requirement and a formation of vesicle in necrosis [34]. Although necrosis is an unprogrammed cell death form, the existence of programmed necrosis types that are regulated by various stimuli and factors has been known.

Necroptosis is a programmed and regulated necrosis type that is triggered by tumor necrosis factor receptor-1 (TNFR1) in the presence of caspase inhibition, and also receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and receptor-interacting serine/threonine-protein kinase 3 (RIPK3) take part in this type of necrosis [35-39].

Another type of programmed necrosis, mitochondrial permeability transition (MPT) dependent necrosis, permeability transition pore complex (PTPC), and its component cyclophilin D (CYPD) play a role in this type of necrosis by causing an abrupt increase in the cytoplasmic calcium ions and ROS production so that they induce the MPT [39-44].

Parthanatos is another programmed and regulated necrosis that is related to the AIF translocation, mitochondrial depolarization, PAR polymer synthesis and accumulation, and activation of poly (ADP-ribose) polymerase 1 (PARP1) [45-49].

Pyroptosis is a programmed cell death form that is triggered through the caspase-1 inflammasome pathway, that is observed alterations in the morphology such as pore formations on the cell membrane, swelling cytoplasm, and disruption of the membrane [50-54].

Ferroptosis is another programmed, and iron-dependent cell death form that differs from apoptosis, necrosis, and autophagy because of the changes in the morphology of mitochondria such as shrinkage in the mitochondria and degradation of Krista [55-58].

5. Glycosylation, Fucosylation, Sialylation, and Abnormal Glycosylation

Glycosylation, which is also called protein glycosylation, is a post-translational maturation process of proteins by glycosyltransferases and glycosidases located in the Golgi apparatus and endoplasmic reticulum by adding or removing carbohydrate moieties. There are two major glycosylation patterns, the N-linked glycosylation that occurs on Asn residue in the Asn/X/Ser sequence, and the O-linked glycosylation that occurs on Ser or Thr residues. However, the X in the sequence of Asn/X/Ser cannot be proline. Especially in eukaryotes, the nucleotide donors conjugated with carbohydrates such as cytidine monophosphate (CMP)-sialic acid, uridine diphosphate (UDP)-glucose, guanosine diphosphate (GDP)-fucose, or etc., are the primary sources of carbohydrates that requisite for glycosylation [59].

Fucosylation and sialylation are the sophisticated modification process of glycans that the glycans are formed into more complex structures by adding fucose or sialic acid moieties through fucosyltransferases and sialyltransferases, respectively [59,60]. Not only are fucosylation and sialylation related to biological functions, but also to cancer [60-63].

Abnormal glycosylation is the glycosylation alteration in cancer cells, occurs because of the alteration in glycosylation motif and factors, and presents tumor-associated and aberrantly expressed glycans or glycoprotein structures in cancer cells. These factors can be the over-expression of the glycosyltransferases and glycosidases, the change in the levels of nucleotide carbohydrate donors, and the increase in the glycoproteins that contain specific glycan structures. Silsirivanit has stated that these unique glycans and glycoprotein structures or enzyme levels are used for diagnosis, monitoring, screening, staging, and prognosis [59].

6. LECTINS IN CANCER TREATMENT

6.1. *Canavalia ensiformis*

According to Suvarna and Sharma stated, Concanavalin A (ConA) is a lectin specific for mannose/glucose [64,65].

According to Bhutia *et al.* stated, the anti-cancer activity of ConA has been reported to be through deoxyribonucleic acid (DNA) damage, alteration of the mitochondrial membrane potential, and reactive oxygen species (ROS) production [24,66,67]. Also, ConA has been reported to reduce the expressions of distinct signal pathways through nuclear factor-kappa β (NF-kβ), extracellular signal-related kinase (ERK), and c-Jun N-terminal kinase (JNK), and to trigger the apoptosis through the induction of p53 [24,68-70]. Furthermore, ConA has been shown to induce autophagic cell death through BNIP3 and mitochondrial pathway in hepatoma cells [24,71]. Moreover, macrophage migration inhibitory factor (MIF) has been reported to involve in ConA induced autophagic cell death, in hepatoma cells [24,72].

According to Jiang *et al.* stated, ConA has been reported to be a legume lectin that can induce the intrinsic pathway of apoptosis in both human hepatocellular carcinoma HepG2 cells, and melanoma A375 cells [4,66,67].

According to Pervin *et al.* stated, ConA successfully induced the apoptotic morphologies in breast cancer MCF-7 cell line, and reduced the weight and volume of tumor derived from MCF-7 cells *in vivo* in a dose and time-dependent manner [73,74]. Also, in another study, ConA has been reported to cause both apoptotic and autophagic cell death while supporting these cell deaths with ROS production [73,75].

In a study that Suvarna *et al.* performed, ConA was isolated from seed cotyledon of *Canavalia ensiformis*. Subsequently, ConA has been shown to cause apoptotic morphologies, inhibit proliferation in a dose-dependent manner, and increase the cell

population at the sub-G0/G1 phase in MCF-7 cells. Unlike MCF-7 cells, ConA caused no significant inhibition up to 100 μg/mL in HEK293T cells which are normal kidney cell lines [76].

In another study performed by Kar *et al.*, high doses of ConA have been observed to inhibit the viability of C6 glioblastoma cells. Also, high doses of ConA have been reported to trigger apoptosis through oxidative stress, disruption of thiol/disulfide homeostasis. In addition, malondialdehyde has been shown to involve in ConA-induced apoptosis in C6 glioblastoma cells. Also, TNF-α and IL-6 have been reported to increased. The apoptotic mechanism of ConA has been reported to be through the release of cytochrome c and caspase-3 activation, indicating the intrinsic pathway [77].

6.2. *Viscum album*

According to Bhutia *et al.* stated, *Viscum album* L. lectin, which is also called mistletoe lectin (ML), is the Type 2 Ribosome-inactivating Protein (RIP) that can trigger both intrinsic and extrinsic pathways of apoptosis in tumor cells. MLs have been classified into three groups which are ML-I, ML-II, and ML-III [24,78]. The ERK, p38, Akt, and stress-activated protein kinase (SAPK)/JNK have been reported to be regulated by MLs, indicating MLs anticancer activity [24,79-81].

According to Pervin *et al.* stated that the *Viscum album* extract (VAE) treatment at optimal dose has been reported to relieve the symptoms of tumor in a patient stricken with sarcoma, and it has been observed to recovery in symptoms in a patient stricken with adenoid cystic carcinoma [73,82,83]. In a study that used *Viscum album* agglutinin (VAA), Korean VAA has been reported to inhibit successfully proliferation and metastasis in the mice bearing B16-BL6 melanoma cells through apoptosis or type 1 programmed cell death [73,84]. VAA and VAE have been shown to have a cell growth inhibition effect in P815, EL-4, Ke37, MOLT-4, and U937 cells [73,85]. In addition, European *Viscum album* agglutinin (VAA-I) has been reported to trigger apoptosis through increasing cellular ROS and inhibiting the synthesis of proteins, in particular the anti-apoptotic protein Mcl-1 [73,86].

6.3. *Musa acuminata*

In the study that Srinivas *et al.* performed in 2019, phloem exudate of *Musa acuminata* Colla. has been demonstrated to have high lectin activity, stable at 70°C and pH 4-5, and also preserved its activity even at pH 9-10. The viability of EAC cells has been reported to reduce up to %20-%15 after a high dosage of exudate. The proliferation of EAC, HeLa, and MCF-7 cells decreased significantly after treatment. *Musa acuminata* exudate has been reported to inhibit angiogenesis with %80. Additionally, the exudate-induced apoptosis has been demonstrated to be through caspase-3. Srinivas *et al.* reported that *Musa acuminata* has the highest lectin activity compared to other plants evaluated [110].

In another study that Srinivas *et al.* performed, they isolated *Musa acuminata* lectin (MAL), which is specific for D-mannose and is 27-29 kDa, from the pseudostem of the plant. HeLa cells have been reported to be the most sensitive cell line to the cytotoxicity of MAL, compared to other cells assessed, MCF-7, HT-29, K562, and EAC. Additionally, the ability of migration and colony formation of HeLa cells decreased. Cytotoxicity of MAL has been determined to be negligible in normal cells, Chang liver cell line CCL-13. In EAC and HeLa cells, MAL has been reported to trigger apoptosis via the downregulation of Bcl-2, upregulation of Bax, and through caspase-3, caspase-9, and caspase-8, and cause apoptotic morphologies. In addition, MAL has been reported to cause suppression of the phosphorylation of Akt, Jnk, and Erk1/2 pathways in HeLa and EAC cells, indicating that these pathways involved in MAL-induced apoptosis in these cells. 2000 mg/kg (body weight) MAL administration has been reported to cause no death and side effects in test subjects. Also, *in vivo* MAL treatment reduced the tumor weight, and promote the life span up to 45 days. On the other hand, MAL treatment has been demonstrated to suppress neoangiogenesis in both *in vivo* and *in ovo*-CAM model. Notably, the temperature and pH stabilities of MAL are in a correlation with the study carried out in 2019 by Srinivas *et al.* [111].

6.4. *Cephalosporium curvulum*

According to Nagre *et al.* stated, The *Cephalosporium curvulum* is a pathogenic fungus that causes mycotic keratitis [112,113], and *Cephalosporium curvulum* lectin (CSL) has been reported to have an affinity to N-glycans contain α1-6 branches [112,114]. Although CSL can bind to hepatocellular cell line HepG2 and pancreatic cancer cell line PANC-1, its binding efficacy to these cell lines decreased when incubated with mucin. MTT assay has revealed that 20 μg/mL CSL treatment resulted in growth inhibition in PANC-1 and HepG2. In addition, the effects of CSL on cell growth have been demonstrated to be reduced in the presence of mucin. CSL has been reported to trigger apoptosis through the intrinsic pathway by causing the loss of mitochondrial membrane potential, increased ROS production, and increased expression of caspase-3, caspase-9 as well as cytochrome c [115].

6.5. *Egletes viscosa*

According to Gomes *et al.* stated, *Egletes viscosa* (L.) Less. is a plant that belongs to the Asteraceae family, spreads in tropical regions of America, and is used for the treatment of disorders such as stomach pain, diarrhea, indigestion [116-118]. Gomes *et al.* isolated *Egletes viscosa* lectin (EgviL) which is 28,8 kDa from floral capitula of *Egletes viscosa*. EgviL has been reported to have an affinity to galactose and glucose. Its HA was determined to be stable at 30°C-60°C and pH 3-4, with maximum activity at pH 5-6-7. EgviL caused significant cytotoxicity and activate apoptosis in Jurkat E6-1 cells, however, it led to cytotoxicity at only 100 μg/mL in PBMCs [118].

6.6. *Entada rheedii*

According to Naik and Kumar stated, *Entada rheedii* Spreng. is a plant that belongs to the Leguminosae family and spreads in Africa, Australia, and Asia. Particularly in Asia, the liver dysfunctions were treated with the extract of *Entada rheedii*'s various organs [119,120]. In this study that Naik and Kumar performed, *Entada rheedii* lectin was isolated from seeds of *Entada rheedii*. The lectin has been reported to be lactose specific, 20 kDa and in monomeric nature, and significantly agglutinate the human blood group B erythrocytes. Its HA activity has been reported to retain at pH 6-10 and 30°C-60°C. The lectin successfully decreased the viability of HeLa and A549 cells by leading to apoptotic morphologies in a dose-dependent manner, with cause no significant decrease in African green monkey normal kidney cells Vero [120].

6.7. *Phaseolus acutifolius*

In this study that Moreno-Celis *et al.* performed, the LC_{50} values of *Phaseolus acutifolius* A.Gray lectin fraction, which is also called Tepary bean lectin fraction (TBLF), has been reported to be 402 µg/mL, 49.2 µg/mL, and 4.7 µg/mL in HT-29, RKO, and SW-480, respectively. SW-480 was the most sensitive cell line against the effects of TBLF among these cells. Nevertheless, the highest early apoptotic cell population and total apoptotic cell population were observed in HT-29 with no necrotic effects. Also, in HT29 cells, the TBLF caused reduced Bcl-2 expression, increased p53 expression particularly at 4-8 hours, increased phosphorylated p53 expression within the first 8 hours, and compared to control, it increased the total caspase level and caspase-3 and caused cell cycle arrest in G0/G1 phase [121].

6.8. *Microgramma vacciniifolia*

According to Patriota *et al.* stated, *Microgramma vacciniifolia* (Langsd. & Fisch.) Copel. is a plant that belongs to the Polypodiaceae family. *Microgramma vacciniifolia* frond lectin (MvFL) has been reported to have trypsin inhibitor ability and lectin activity [122,123]. In this study that Patriota *et al.* performed, the viability of sarcoma 180 cells was reduced after MvFL treatment. In addition, MvFL treatment (6.25, 12.5 µg/mL) has been reported to significantly increase the early apoptotic cell population. Also, *in vivo* MvFL treatment (10, 20 mg/kg) has been reported to successfully reduce tumor weight compared to control. MvFL has been shown to significantly reduce the vessel diameter, however, only 10 mg/kg MvFL has been reported to reduce the number of secondary vessels. Additionally, the number of primary and secondary vessels have been demonstrated to have no significant changes after both methotrexate (MTX) and MvFL treatment. It has been determined that in the spleen, liver, and kidney, MvFL treatments have not caused toxicity, and these organs preserved their morphologies after MvFL treatments [123].

6.9. *Aspergillus niger*

According to Jagadeesh *et al.* stated, the *Aspergillus* genus contains pathogenic fungus species that could lead to mycotic keratitis [124,125]. Jagadeesh *et al.* isolated the

Aspergillus niger from the corneal smears of a patient that is afflicted with mycotic keratitis, and afterwards the *Aspergillus niger* lectin (ANL) which is specific for fetuin, mucin, and L-fucose was purified from the mycelium of the fungus. ANL has been reported to can agglutinate all human blood groups and rabbit erythrocytes. In addition, ANL was stable at pH 7-10 with optimum activity at pH 7.2. ANL inhibited the cell growth of PANC-1 in a dose and time-dependent manner [125].

In another study that Jagadeesh *et al.* performed, ANL has been reported to inhibit the cell growth of HepG2 and HT-29 cells and cause an increase in early and late apoptotic cell populations in both HepG2 and HT-29 cells. In HepG2 cells, ANL triggered the intrinsic apoptosis via an increased ROS production, the loss of mitochondrial membrane potential, increased release of the cytochrome c, and raised expression levels of active caspase-9 and caspase-3 [126].

6.10. *Adenia kirkii*

In this study that the lectin substances of *Adenia kirkii* (Mast.) Engl. were researched and *Adenia kirkii* lectin (Kirkiin) has been reported to be a Type 2 RIP. It was observed that the HA activity of *Adenia kirkii* lectin was higher than the other toxins from the plants that belong to *Adenia* genus. However, it has been determined that *Adenia kirkii* had two lectin substances that are formed in single-chain and double-chain, and the capability of protein synthesis inhibition of double-chain lectin was more effective and stronger than single-chain lectin. Therefore, the double-chain lectin was called Kirkiin. The ability of inhibition on protein synthesis in the mammalian ribosomes and *Saccharomyces cerevisiae*'s ribosomes of Kirkiin has been reported to be due to its N-glycosylase, and rRNA N-glycosylase activity, respectively. In addition, Kirkiin was more effective in inhibiting the protein synthesis in the neuroblastoma NB100 cell line than another Type-2 RIP, the Ricin. Moreover, Kirkiin induced apoptosis in NB100 cells [129].

6.11. *Artocarpus hypargyreus*

In this study that Zeng *et al.* performed, *Artocarpus hypargyreus* Hance lectin (AHL) was isolated from seeds of *Artocarpus hypargyreus*. AHL has been demonstrated to have an affinity to methyl-α-D-mannose, methyl-α-D-galactose, and GalNAc. Also, AHL has been determined to be glycoprotein due to its percentage of carbohydrate that contains. Additionally, AHL was stable at 0°C-40°C, with optimal activity at pH 5-9. AHL has been reported to have an immunomodulatory activity through the activation of human T lymphocytes and the release of cytokines such as interferon-gamma (IFNγ), TNF-α, and IL-6 [132].

In another study that Luo *et al.* performed, AHL has been determined to have a mannose-binding domain and belong to the Jacalin lectin family. AHL has been reported to bind to Jurkat T cells strongly and cause apoptotic morphologies such as nuclear fragmentation and condensation in the cells that undergo apoptosis. AHL-induced apoptosis in Jurkat T cells occurred through increased phosphorylation of ERK1/2 and p38, raised expressions

of Bad and Bax, the activation of caspase-3, and the poly (ADP-ribose) polymerase (PARP) cleavage [133].

6.12. Other lectins

According to Pervin *et al.* stated, the ricin is a lectin isolated from *Ricinus communis* L., and has been reported to have a cytotoxic effect owing to its ribonucleic acid (RNA) N-glycosidase activity which is within the A-chain of ricin [73,87]. In a study that the immunotoxins containing an A-chain of ricin were used, the tumor growth of the MOLT-4 human T-cell leukemia cells in mice was reduced after the treatment [73,88].

According to Pervin *et al.* stated, *Pisum sativum* lectin has been shown to decrease the growth of EAC cells through increased expression of Bax and decreased expression of Bcl-2, indicating apoptotic cell death, also arrest the cell cycle at the G_2/M phase [73,89].

According to Pervin *et al.* stated, the highest dose of *Lycoris aurea* (L'Héritier) Herbert. agglutinin (LAA) has been shown to reduce the tumor weight and volume through apoptosis after 14 days of treatment in mice that are bearing tumors derived from A549 cells [73,90]. According to Bhutia *et al.* stated, in A549 cells, apoptosis was activated by LAA via the inhibition of the PI3K-Akt pathway. Also, LAA has been reported to cause cell cycle arrest at the G_2/M phase [24,90].

According to Pervin *et al.* stated, intraperitoneally administration of *Momordica charantia* L. lectin (MCL) which is specific for D-galactose has been shown to inhibit the growth of EAC cells through cell cycle arrest at the G_0/G_1 phase in a dose-dependent manner. However, no apoptotic morphologies have been observed in EAC cells after MCL treatment [73,91].

According to Bhutia *et al.* stated, *Sophora flavescens* Aiton. lectin (SFL) has been reported to be mannose-specific and induce apoptosis through the caspase-dependent pathway in HeLa cells in a dose and time-dependent manner, and the HeLa cells were exposed to significant cytotoxicity caused by SFL [24,92].

According to Bhutia *et al.* stated, *Abrus precatorius* L. abrin (ABR), and *Abrus precatorius* agglutinin (AGG) which is less toxic than ABR have been reported to be type II RIP and specific for galactose [24,93,94]. Non-lethal doses ABR triggered apoptosis through the intrinsic pathway in various cancer cell lines due to its significant cytotoxicity [24,93,95]. AGG has been reported to trigger apoptosis via activation of both intrinsic and extrinsic pathways through the Akt-ROS-dependent pathway in breast cancer cell lines. Additionally, in HepG2 cells, AGG induced apoptosis through inhibition of NF-kß and Heat shock protein-90 (Hsp-90) to lead to activation of caspases [24,94,96].

According to Bhutia *et al.* stated, *Allium sativum* L. lectin has been reported to be a lectin that specific for mannose, and that can trigger apoptosis in U937 and HL60 cells [24,97].

According to Bhutia *et al.* stated, PCL has been reported to have significant anticancer activity, with lower cytotoxic effects in normal cells [24,98]. PCL has been demonstrated to trigger the intrinsic pathway of apoptosis in A375 melanoma cells, and also trigger apoptosis in L929 cells [24,99,100]. In addition, PCL activated apoptosis by causing ROS production through activation of mitogen-activated protein kinase (MAPK) and NF-kß pathways in A549 cells [24,101].

According to Bhutia *et al.* stated, *Polygonatum odoratum* (Mill.) Druce. lectin (POL) has been reported to be a lectin that specific for mannose. In L929 cells, it has been shown to trigger caspase-dependent and TNF-α induced apoptosis [24,102]. In another study, in A549 cells, POL triggered apoptosis by leading the release of cytochrome c, the activation of caspase-3 and caspase-9, the downregulation of Bcl-2 and Bcl-Xl, and the upregulation of Bax and Bid [24,103].

According to Bhutia *et al.* stated, *Triticum vulgaris* L. lectin, which is also called Wheat germ agglutinin (WGA), has been reported to be a lectin that specific for GlcNAc, sialic acid/neuraminic acid, and also it contains a hevein domain [24,104]. In another study that Wang *et al.* performed in osteosarcoma, melanoma, and hepatoma cells, WGA has been reported to trigger apoptotic morphologies and inhibit the growth of the cells [24,105].

According to Bhutia *et al.* stated, *Solanum tuberosum* L. lectin is a lectin that is specific for GlcNAc, and that can inhibit the growth of EAC cells [24,106].

According to Bhutia *et al.* stated, in CNE-1 cells, *Setcreasea purpurea* Schum. lectin has been reported to possess cytotoxic activity, and trigger apoptosis in a dose and caspase-dependent manner [24,107].

According to Bhutia *et al*. stated, *Artocarpus heterophyllus* Lam. lectin has been reported to be a lectin that specific for α-D-mannose, and that can interact with the N-glycans that contains ß-1,6-GlcNAc branches and activate apoptosis in myeloid leukemia NB4 cells [24,108].

According to Bhutia *et al.* stated, *Morus alba* L. lectin has been reported to induce apoptosis in a caspase-dependent manner in MCF-7 and HCT-15 cells [24,109].

Canavalia gladiata (Jacq.) DC. lectin, which is also called Concanavalin G (ConG), was isolated from seed cotyledon of *Canavalia gladiata*. ConG caused apoptotic morphologies in MCF-7 such as nuclear fragmentation, chromatin condensation and successfully inhibited the proliferation of MCF-7 cells in a dose-dependent manner. In contrast to MCF-7, ConG led to negligible inhibition in normal human embryonic kidney HEK293T cells [76].

Praecitrullus fistolsus lectin (Pfl) was isolated from the fruit of *Praecitrullus fistulosus*. Pfl has been shown to agglutinate erythrocytes, and cause significant cytotoxicity in HT29 by inducing apoptosis through the caspase-3-dependent pathway. In contrast, Pfl

caused negligible cytotoxicity in peripheral mononuclear blood cells (PBMCs). Pfl has been reported to suppress the colony formation ability of HT29 and can control the cell migration compared to the control group [6].

In this study that Akev *et al.* performed, the lectin from *Aloe vera* (L.) Burm. f. (Aloctin) was isolated from the leaf skin of the plant. Fetuin and avidin have been reported to lead to a significant inhibition in the HA activity of Aloctin [127]. Aloctin has been reported to cause significant cytotoxicity in the gastric adenocarcinoma AGS cell line and human osteosarcoma Saos-2 cell line compared to other cancer cell lines. In addition, it has been evaluated that the potential use of Aloctin with Imatinib (IM) against AGS and Saos-2. 1 µg/mL Aloctin + 50 µM IM treatment reduced the viability of AGS cells (%9.66) compared to only IM treatment. Also, 0.5 µg/mL Aloctin + 25 µM IM and 1 µg/mL + 50 µM IM treatments reduced the viability of Saos-2 cells compared to 25 µM and 50 µM IM treatments. However, Annexin V/PI-FITC and flow cytometry analysis revealed that Aloctin triggered neither apoptotic nor necrotic cell death [128].

In this study that Hung and Trinh performed, they isolated a new lectin which is called *Kappaphycus striatus* (F.Schmitz) L.M.Liao lectin (KSL) from a red alga, the *Kappaphycus striatus*. Additionally, the HA of the KSL was inhibited by only yeast mannan, indicating that the lectin has an affinity to high-mannose type N-glycans. The cytotoxic effects of KSL were evaluated in the cell lines, HT-29, HeLa, MCF-7, AGS, and SK-LU-1. In conclusion, SK-LU-1 has been demostrated to be the most sensitive cell line to effect of the KSL. Also, the cytotoxic effects of KSL in the cell lines were inhibited by yeast mannan [130].

Liparis nervosa (Thunb.) Lindl lectin (LNL) was isolated from the rhizomes of the *Liparis nervosa*. LNL has been reported to be in a phylogenetic correlation with the lectin from *Epipactis helleborine* (L.) Crantz. The HA of LNL was stable at 20°C-50°C and pH 7-8. However, it has been reported that the HA has been inhibited in the presence of D-mannose, GlcNAc, and thyroglobulin. The viability of H1299 and HeLa cells decreased in a dose-dependent manner after LNL treatment. In addition, pyknosis or DNA fragmentation have been observed in H1299 that treated with LNL, indicating that LNL activates apoptosis in H1299 cells. Also, LNL has been reported to belong to *Galanthus nivalis* L. agglutinin (GNA) family, and LNL has been considered to have mannose-binding motifs "QXDXNXVXY" possess three mannose-binding docking points, which are for mannose, mannobiose, and mannotriose [131].

Rashidbaghan *et al.* isolated *Urtica dioica* L. agglutinin (UDA) from the extract obtained from roots and rhizomes of the plant. The trypsin-treated human erythrocytes have been observed to be agglutinated after 20 µg/mL UDA treatment. UDA reduced the viability of acute myeloid leukemia HL-60 cell line in a dose-dependent manner and triggered the intrinsic pathway through the activation of caspase-3, caspase-9, and partially caspase-8 [134].

Elamine *et al*. determined that the *Vicia palaestina* lectin (VICPALA) isolated from seeds of the *Vicia palaestina* belongs to the single-chained legume lectin family and specific for GalNAc. The 50 and 75 µg/mL VICPALA treatments for 3 and 4 days have been reported to inhibit the proliferation about %20-%70 in Caco-2 cells. Also, the 75 and 100 µg/mL VICPALA treatments for 3 and 4 days have been reported to inhibit the proliferation of THP-1 cells [135].

In a nutshell, the cell death of cancer cells can be induced by lectins owing to their affinity to carbohydrates residues which are highly expressed on cancer cells. Various lectins with distinct binding properties that induce cell death of distinct cancer cell lines through different cell death forms have been shown in Table 1.

Table 1. Summary of lectins that could successfully induce cell death mechanisms in cancer cell lines

Lectin	Cell Lines	Cell Death Types
ConA	HepG2, A375, MCF-7, C6 Glioblastoma, and Hepatoma cells*	Apoptosis, Autophagy* [4,24,66,67,71,73,74,76,77]
Korean VAA	B16-BL6 Melanoma	Apoptosis, Type 1 Programmed Cell Death [73,84]
MAL	EAC, HeLa, and MCF-7	Apoptosis [110,111]
CSL	PANC-1 and HepG2	Apoptosis [115]
EgviL	Jurkat E6-1	Apoptosis [118]
Entada rheedii Lectin	HeLa and A549	Apoptosis [120]
TBLF	HT-29	Apoptosis [121]
MvFL	Sarcoma 180	Apoptosis [123]
ANL	HepG2 and HT-29	Apoptosis [126]
Kirkiin	NB100	Apoptosis [129]
AHL	Jurkat T Cells	Apoptosis [133]
Pisum sativum Lectin	EAC	Apoptosis [73,89]
LAA	A549	Apoptosis [24,73,90]
SFL	HeLa	Apoptosis [24,92]
AGG	HepG2	Apoptosis [24,94,96]
Allium sativum Lectin	U937 and HL60	Apoptosis [24,97]
PCL	A375, A549, and L929	Apoptosis [24,99,100,101]
POL	A549 and L929	Apoptosis [24,102,103]
Setcreasea purpurea Lectin	CNE-1	Apoptosis [24,107]
Artocarpus heterophyllus Lectin	NB4	Apoptosis [24,108]

Morus alba Lectin	MCF-7 and HCT-15	Apoptosis [24,109]
ConG	MCF-7	Apoptosis [76]
Pfl	HT29	Apoptosis [6]
Aloctin	AGS and Saos-2	**Unknown** [128]
LNL	H1299	Apoptosis [131]
UDA	HL-60	Apoptosis [134]

7. LECTINS IN CANCER DIAGNOSIS

Lens culinaris Medik. agglutinin (LCA) has been reported to be a convenient lectin that can recognize the increased levels of α-fetoprotein (AFP) in hepatocellular carcinoma (HCC). However, not only can AFP levels increase in HCC, but also in cirrhosis and liver failure [73,136]. Therefore, AFP-L3 isoform which possesses α-1,6 fucose in GlcNAc moiety, strongly reactive with LCA, can be used to distinguish HCC from other liver diseases [73,137-139].

ConA reactive species of AFP have been reported to be less in patients with liver metastasis than HCC and other liver diseases [73,136]. Additionally, *Phaseolus vulgaris* L. agglutinin has been demonstrated to be a convenient lectin that can be used to distinguish HCC from other liver diseases [73,137].

Frutalin is a recombinant lectin that is isolated from *Artocarpus incisa* L. and has been reported to recognize human prostate cancer cells [24,140,141].

Phaseolus vulgaris phytohemagglutinin has been reported to can be used to diagnose colon and pancreatic cancer [12,142,143].

Wisteria floribunda (Willd.) DC. agglutinin has been reported to play a role to diagnose intrahepatic cholangiocarcinoma due to its ability to interact with L1 cell adhesion molecule (L1CAM) [12,144].

Ricinus communis agglutinin is a lectin that can be used to diagnose triple-negative breast cancer (TNBC) with the aid of binding to a membrane glycoprotein which is POTE ankyrin domain family member F (POTEF), and also to predict the percentage of metastasis [12,145].

CSL, which has specificity to glycans contains α1-6 fucose moiety, has been reported to successfully recognize differences of AFP levels in HCC between normal cases. Therefore the CSL can be useful for diagnosing and treating patients with HCC [115].

In a study that Jagadeesh *et al.* performed, ANL has been reported to successfully binds to primary and metastatic colon cancer tissues, and detects fucosylated-AFP in HCC patients' serum [126].

In a study that Ganatra *et al.* performed, *Boletopsis grisea*, a fungus that spreads in North America and Scandinavia, and its lectin was cloned in *Escherichia coli* to produce a recombinant *Boletopsis grisea* lectin (rBGL). Subsequently, rBGL has been determined to be a lectin that 15 kDa molecular weight with specificity for GalNAc and GlcNAc. Additionally, rBGL had an affinity to sialylated and sulfated O-linked mammalian glycans that contain Galβ1,3GalNAc-α, and N-linked glycans that contain β-GlcNAc. Nevertheless, these binding properties of rBGL to sialylated and sulfated O-linked mammalian glycans were reduced as long as the glycan has not 6-sulfate [146].

Choi *et al.* conjugated sialic acid-specific *Sambucus nigra* agglutinin (SNA), glucose/mannose-specific ConA, and fucose-specific *Alueria aurantia* lectin (AAL) with Janus nanoparticles (JNP) to determine their potential utilization for cancer diagnosis. The lectin-JNP conjugates, AAL-JNP and SNA-JNP has been reported to successfully determine PANC-1 cell line. The lectins have been demonstrated that they play the main role to recognize cancer cells by an assay with bare JNPs have been performed. In an assay that contains various pancreatic cancer cell lines such as MIA PaCa-2, AsPC-1, Capan-2, and normal pancreas epithelial H6C7 cell line, the AAL-JNP has been reported to binds all of the cancer cell lines and has more affinity to PANC-1, while SNA-JNP has been reported to have more affinity to MIA PaCa-2 cell line than PANC-1. In an assay performed with Exo-Chips, AsPC-1 exosomes have been reported to get caught less than other exosomes of cancer lines by AAL-JNP and SNA-JNP because of their metastatic property, indicating that these lectin-JNP conjugates can determine the metastatic characteristics. A clinical experiment that contains metastatic and non-metastatic pancreatic cancer groups performed with Exo-Chips has been revealed that the exosomes in the blood plasma caught by lectin-JNP and that AAL-JNP is effective in cancer diagnosis and determining the metastatic characteristics [147].

According to Teeravirote *et al.* stated, *Butea monosperma* agglutinin (BMA) was isolated from the seeds of *Butea monosperma* and is specific for galactose and GalNAc [148-150]. In a study that Teeravirote *et al.* performed, it was aimed that recognize the *Butea monosperma* agglutinin-associated glycans (BMAG) in serums and tissues of patients with cholangiocarcinoma. The BMAG expressions have been shown to be higher in hyperplastic and dysplastic bile duct, and cholangiocarcinoma tissue. In addition, the different BMAG expression levels were determined between tissues obtained from the patients with cholangiocarcinoma. However, in the hamster model that bearing cholangiocarcinoma through *opisthorchis viverrini* infection, the BMAG expressions were found to higher in cholangiocarcinoma than hyperplastic and dysplastic bile duct. Notably, BMAG expressions were found to be higher in serums of patients with cholangiocarcinoma, compared to serums of patients with hepatoma. Moreover, BMAG expressions have been reported to decrease after removing out the tumor by surgical intervention. Consequently, the higher BMAG expressions have been reported to indicate a poor prognosis compared to the lower BMAG expressions [150].

Consequently, lectins can be convenient diagnostic tools for cancer due to their binding affinities to different cancer biomarkers that possess carbohydrate moieties, and their dissimilarity in terms of recognition affinity can make them utilized for a broad range of cancer types. Some of the candidate lectins have been summarized in Table 2. Furthermore, they can take place in the prediction of metastasis.

Table 2. Lectins that can involved in cancer diagnosis

Lectin	Affinity/Interaction	Cancer Type
LCA	AFP and AFP-L3	HCC [73,136-139]
ConA	AFP	HCC [73,136]
Phaseolus vulgaris Lectin	AFP	HCC, Colon, and Pancreatic Cancer [12,73,137,142,143]
Wisteria floribunda	L1CAM	Intrahepatic Cholangiocarcinoma [12,144]
Ricinus communis Agglutinin	POTEF	TNBC [12,145]
CSL	AFP	HCC [115]
ANL	AFP-L3	Primary and Metastatic Colon Cancer [126]
Conjugated AAL	Fucose Residues	PANC-1, MIA PaCa-2, AsPC-1, and Capan-2 [146]
Conjugated SNA	Sialic Acid Residues	PANC-1, MIA PaCa-2 [146]
BMA	BMAG	Cholangiocarcinoma [150]

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Conflicts of Interest
The authors declare no conflict of interest.

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