[Frontiers in Bioscience 13, 1130-1140, January 1, 2008]

Uses of plant lectins in bioscience and biomedicine

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1. ABSTRACT

New research directions in the last decade have led to major developments in the uses of plant lectins in bioscience and biomedicine.Major advances have been made in our understanding how lectins in the diet can act on the gastrointestinal tract and the physiological consequences of their actions, and how they can modulate body- and organ metabolism, the immune system and the gut microflora.Particularly striking progress has been made in unravelling the effects, often beneficial, of both orally- and parenterally administered lectins, including lectins of *Viscum album-, Phaseolus vulgaris-, Robinia pseudoacacia*, *Agaricus bisporus*, etc on tumours and in cancer therapy.Results have also made it possible to devise and try out other beneficial applications of plant lectins as gut-, metabolic- and hormonal regulators, immune reagents, probiotic/prebiotic oral supplements and to develop methods based on the oral application of lectins to protect the intestines against the often lethally harmful effects of chemo- and radiotherapy.With the development of genetically modified (GM) plants by transferring the genes of some of the natural insecticidal lectins such as the various *Bacillus thuringiensis* lectin-Cry toxins or some insecticidal plant lectins to major crop plants, a possible new avenue in plant protection may have opened up.

2. INTRODUCTION

It was well over a century ago that Stillmark discovered ricin in aqueous extracts of castor bean (*Ricinus communis*), a highly toxic lectin and thus laid the foundation of what we now call the field of lectinology.The interest in lectins was helped along over the years by a number of early discoveries, such as that not all lectins were as toxic as ricin, and that some lectins agglutinated human erythrocytes in a blood group specific manner within the ABO blood group system and, most importantly, that the basis of this reactivity was that lectins were capable of specifically recognizing discreet carbohydrate structures and reversibly binding to them.These discoveries by a dedicated but relatively small number of scientists have helped to maintain the interest in these carbohydrate-reactive plant proteins.However, what has made this, a somewhat esoteric topic in many scientists' view, into a major branch of science was the result of three major discoveries.Thus, it has been shown that lectins as signalling proteins not only occur in plants but that they are important constituents of all living matter, including humans.An equally important discovery was that due to their high and specific reactivity with carbohydrate epitopes regardless whether these were in solution or on cellular surfaces, lectins could offer the possibility of

developing useful tools and applications in bioscience and biomedicine.Finally, it was realized that plant lectins were naturally occurring insecticidal proteins and were thus probably one of the major components of the defensive system of plants protecting them against insect pests.With the advent of the recombinant DNA technology it became possible to transfer insecticidal lectin transgenes by genetic engineering to crop plants without such protection and thus make them resistant to insect attacks.The success of this discovery can be measured by the birth of a new industry, producing genetically modified (GM) plants on a commercial scale, the GM-biotechnology industry.

It needs to be pointed out here in the introduction that this review will not discuss the substantial progress made in the last few years to unravel the roles and many possible functions of lectins in plants but, with a heavy emphasis, it will concentrate on describing and discussing possible promising bioscience and biomedical uses of mainly plant lectins.It is felt that the major developments that have taken place in deciphering the many important roles of animal lectins, particularly the much studied serum mannose binding lectin and galectins and their involvement in human disease such as rheumatoid arthritis and possible medical applications (for references () should be dealt with separately, unless their actions in contributing to the effectiveness of plant- or bacterial lectins in biomedicine makes it necessary to describe them.

3.LECTINS IN BIOSCIENCE AND MEDICINE

3.1. Applications of lectin-cell interactions

3.1.1.Lectins as gut stimulants

Practically all plant lectins are resistant to varying degrees to gut proteolysis (6,7) and therefore remain biologically active during their passage through the gastrointestinal tract.The lectin effects on the gut, body metabolism, immune and endocrine systems and the bacterial flora are therefore the direct consequence of their interaction with the highly glycosylated receptors of the epithelial surface cells of the gut.This occurs not only in mammals and birds but also in fish, such as the Atlantic salmon and Rainbow trout (8).As glycosylation is different in different compartments of the gastrointestinal tract the same lectin can have diverse effects in different parts of the gut.Plant lectins can also modify the glycosylation of the gut surface cells.Thus, from understanding the molecular and cellular mechanism of their interactions with the gut, it may be possible to utilise lectins as reagents for various nutritional or medical applications (9).

Some plant lectins, such as kidney bean (*Phaseolus vulgaris*) agglutinin (PHA) (10) mistletoe (*Viscum album*) lectin (ML) (11) and many others are well-known mimics of endogenous growth factors, growth hormones and cytokines for a great variety of cell types.Although the lectin binding site is not the normal functional binding site of the transmembrane glycoproteins of cell surface receptors but lectins, by binding to the glycosyl side chains on these glycoproteins spanning the membrane, can induce similar conformational changes to that induced by their natural ligands.Lectins, such as PHA avidly bind to the small intestinal epithelium and are thus potent hyperplastic growth factors, enlarging the crypts, increasing crypt cell number, their production rate (CCPR) and the turnover of epithelial cells.Such plant lectins given orally induce the release of gut peptide hormones that are needed for the normal functioning of the gastrointestinal tract.As a result, plant lectins have been shown to have potentially important clinical applications, such as their use to reverse the grave condition of small bowel atrophy in parenterally fed patients (12).Similar, but not the same, effects result from the intravenous infusion in rats of peanut (*Arachis hypogaea*) agglutinin (13).In another potentially important oral application PHA can be used for the suppression of gastric acid secretion.It is particularly useful that at the same time PHA stimulates the release of cholecystokinin (CCK), leading to increased pancreatic enzyme secretion into the duodenum (14-16), significantly aiding food digestion.Some lectins, such as PHA can also be used to modulate food consumption and gastric emptying in experimental animals (17).PHA has been demonstrated not only to induce the growth of the gastrointestinal tract but also help its maturation in suckling rats (18).With this application it may be possible to eliminate the often-lethal problems that occur in animals on weaning and exposure to adult feeds.PHA and wheat (*Triticum vulgare*) germ agglutinin have also been shown to reduce the levels of heat shock proteins in gut epithelial cells (19).It may also be possible to use PHA as a dietary adjunct or therapeutic agent to stimulate gut function and ameliorate obesity not only in animals but also in humans if a safe and effective dose-range can be established in clinical trials (20).Somewhat similar observations have also been made with soybean whey of high lectin content (21).Many plant lectins, including PHA, are strong stimulants of pancreatic growth and its enzyme secretion (22).Many useful reviews on the effects of plant lectins and trypsin inhibitors have been published (23,24).Unfortunately, even though some of the earlier findings with plant lectins as gut-reactive agents that have biomedical potential have been corroborated by more recent studies (25-27), the development of major pharmaceutical agents or drugs to capitalize on these discoveries has been disappointingly slow.Progress in establishing new lectin-targeted drug delivery systems (28) has also been making slow progress even though the principles of this method of great potential has been worked out quite some time ago.

3.1.2. Dietary lectins

Studies on the effectiveness of palaeolithic diets on human well-being have thrown new light on the possible involvement of lectins, particularly cereal lectins in the aetiology of human diseases as diverse as rheumatoid arthritis, acne, cardio-vascular disease, etc (29).As cereal- and legume lectins increase the permeability of the human gut to bacterial and dietary antigens, peptide fragments derived from milk and cereal grain proteins that have considerable amino acid homologies to collagenous tissues in the synovium and that are capable of stimulating T-cells in an HLA restricted manner (HLA in humans nucleated cells represents the major histocompatibility complex class I molecules) can gain access to the systemic circulation.The

persistent stimulation of the immune system by these exogenous peptides mimicking HLA-derived and self tissue peptides may break the immune tolerance leading to rheumatoid arthritis in sensitive individuals.It was proposed (29) that by eliminating lectins from the diet that have such adverse effects peripheral antigenic stimulus will be reduced and disease symptoms in some patients with rheumatoid arthritis may thus be alleviated.Furthermore, as cereal-based diets rich in lectins were shown in pigs to cause leptin- and insulin resistance their exclusion from the diet could have such beneficial health effects as lowering the level of C-reactive proteins and blood pressure (30,31).Indeed, palaeolithic diets were shown to be superior to even mediterranean diets in improving glucose tolerance in individuals with ischaemic heart disease (32).There have been many attempts to correlate dietary lectins with particular human diseases, particularly with allergies.The early attempts, most notably by Nachbar and Oppenheim (33) and somewhat later by Laura Power (34) have unfortunately not been followed up by clinical studies.The suggested link, however, between various human diseases and disorders and the presence of blood group-specific lectins with specificities within the ABO system in the human diet by D'Adamo (35) has not been scientifically properly established.

3.1.2.1.Effects on tumours

Plant lectins given orally can have diverse effects on different tumours.Thus, it has been shown that the galactose-specific peanut agglutinin, PNA, stimulates cell proliferation in colonic explants in vitro (36) and eating peanuts increases rectal proliferation in individuals with mucosal expression of the peanut lectin receptor (37).In an investigation of the lectin/galactose hypothesis it was shown that the protective effect of fruit and vegetable fibres in colonic cancer is possibly linked to their galactose content.Cereal fibres, on the other hand, contain no galactose and as such have no such protective effect (38).Rather interestingly, of all the non-toxic dietary lectins that preferentially bind the TF (Thomsen-Friedenreich) oncofetal blood group disaccharide (galactose β1,3 N-acetylglucosamine α-) PNA stimulates colonic proliferation while the mushroom (Agaricus bisporus) lectin (ABL) is antiproliferative.However, for this effect ABL needs to be internalised.The lectin then selectively blocks the classical nuclear localization sequence-dependent nuclear protein import (39), but it is not clear whether this is involved in the lectin's antiproliferative effect.The involvement of mucosally adherent bacterial lectin/adhesins in the pathogenesis of Crohn's disease and colon cancer has also been demonstrated.Again, soluble plant fibres that inhibit this adherence have therapeutic potential (40).

In further studies (41) significant progress has been achieved in our understanding of the reaction mechanism of peanut lectin effect.It was shown that the mitogenic peanut lectin was bound to the cell surface TF antigen expressed by the high molecular weight isoforms of the transmembrane glycoprotein CD44 that are generated in neoplastic colonic epithelial cells.This starts up a chain reaction in which the phosphorylation of the hepatocyte growth factor receptor c-Met is increased followed by the downstream activation of p44/p42 mitogen activated protein kinase MAPK.It was a highly significant finding that asialofetuin completely blocked this phosphorylation.This may therefore explain why the binding of dietary, microbial and/or endogenous galactose-binding lectins could affect the proliferation in the cancerous or precancerous colon (41).Further studies corroborated the important role circulating galectin-3 may play in cancer metastasis by showing that a major transmembrane mucin protein (MUC1) overexpressed and aberrantly glycosylated in epithelial cancer is a ligand for galectin-3 via TF and that this endogenous lectin promotes cancer cell adhesion to the endothelium by epithelial adhesion molecules that are otherwise concealed by MUC1 (42).Indeed, there is overwhelming evidence that changes in glycosylation are associated with cancer and chronic inflammation (43) and this gives hope for the future that with further progress in devising new therapeutic and diagnostic strategies the glycan structures characteristic for the various diseases could be specifically targeted (44, 45).Overall, the works of the Rhodes group and others have clearly demonstrated the usefulness of fundamental glycan/lectin studies for developing drugs and therapies to reverse or prevent the progression of certain types of cancers.In fact, lectin markers have long been used in the diagnosis of cancers and other diseases.There are too many recent examples to list them all but a few could be mentioned (46, 47).

3.1.2.2. Possible roles of orally administered lectins in cancer therapy

In a different approach it was shown that orally given kidney bean lectin, PHA, or mistletoe lectin, ML-1, significantly reduced, and in some cases eliminated the development of tumours in NMR and Balb/c mice into which Krebs II ascites tumour cells had been intraperitoneally or subcutaneously injected before the lectin treatment (11, 48-50).ML-1 (250 mg/kg bodyweight/day) fed to mice reduced the mitotic activity in tumours by 75% and the nuclear area was diminished by 21%.Lymphocyte infiltration (CD3 positive cells) in the tumour doubled in these mice and the tumours had shown a high incidence of apoptotic bodies.All these changes were consistent with a major reduction in tumour mass.Indeed, in four out of fifteen mice fed ML-1 for 11 days there was no longer evidence of viable tumour (11).The beneficial lectin effect was complex and due to several factors.These included a deprivation of nutrients of the growing tumour by the high nutrient and polyamine requirements of the lectin-induced compulsory gut growth, inhibition by ML-1 of angiogenesis in the growing tumour and stimulation of the immune system combating the tumour growth.The capacity of various A-B toxin-lectins, including *Bacillus thuringiensis* (Bt) Cry1Ac protoxin to stimulate and modulate both the systemic and mucosal immune systems is now firmly established (51-55).In a more recent study the cellular immune response induced by Cry1Ac and its mutants in mice has been analysed (56).It was shown that the production of Th1 and Th2 type cytokines by Cry1Ac toxins was inhibited by N-acetylgalactosamine, in accordance with the lectinic properties of this Bt toxin.

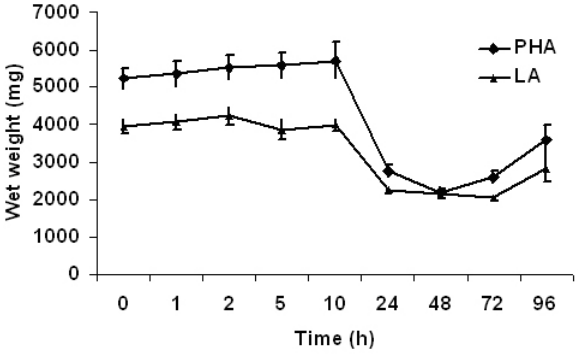

Figure 1.Effect of kidney bean lectin (PHA) pre-treatment on the small intestinal wet weight of 5-fluorouracil (5-FU)-injected rats.Eighteen groups of five rats (approximately 100 g each) were given 10 g of high-quality control diet based on 10% lactalbumin (LA) protein each day for three days.Forty five rats of the test group were intragastrically intubated with 20 mg of PHA daily for three days, while forty five control rats were intubated with 0.9% saline.At 0 time all rats were injected with 150 mg/kg body weight 5-fluorouracil (5-FU) after which they were given the high-quality control (LA) diet for four days.All animals were pair-fed by about 7 g of diet per day.The rats were sequentially killed, five rats of each group at the indicated times, up to 96 hours, their small intestines were excised, rinsed, washed and weighed.

3.1.2.3. Use of plant lectins in the prevention of mucositis

In cancer patients mucositis (diarrhoea, in combination with interference with the integrity and turnover and structure of the gut epithelium, loss of epithelial surface cells mainly by apoptosis, insufficient digestive/absorptive function and deterioration of body metabolism), is a life-threatening condition following radio-, and chemotherapy.Most known growth factors, such as EGF, TGF, IGF or others promise only limited success to prevent this condition, because they are diluted in blood circulation, and spread over all organs of the body without properly targeting the gut tissue.In contrast, the use of agents, such as plant lectins, looks promising as they can be administered orally, are resistant to degradation in the gut and have exclusive effects on the gut as the target organ.Therefore, the effect of two plant lectins, known to induce extensive growth of the gut, such as PHA and RPA from *Robinia pseudoacacia*, were tested on rats which were orally dosed with 5-fluorouracyl (5-FU, a mitotic agent frequently used in chemotherapy), to see whether they can prevent, or at least alleviate the symptoms of mucositis in animals.

Rats were intragastrically intubated with different doses of these lectins before, during, and following chemotherapy with a single dose of 150mg/kg body weight 5-FU *i.p.*It was found that the application of the lectins concurrent with the chemotherapeutic agent did not prevent the damage to the intestinal tissue that was caused by 5-FU.When the lectins were used following the 5-FU treatment, the deterioration of the gut was even more serious.It was established, that the most successful treatment regime to protect the gut from the effect of chemotherapeutic agent was a 3 to 5 days pre-treatment of the rats with the optimal dose of 0.2 g PHA or RPA per kg body weight before starting the chemotherapy, and stopping the lectin application just before the 5-FU treatment.Apparently, after the inducement of hyperplastic growth of the small intestinal epithelium by lectins significantly more functional crypt cells survive ready to restore normal or close-to-normal intestinal structure and function than in non-lectin pre-treated animals (Figures 1 and 2).The rats pre-treated with PHA or RPA for three days, given the chemotherapeutic agent and then fed for four days with a good control diet regained their appetite and their body weight became close to that of the untreated (non-5-FU-injected) animals.Even simple weight measurements of the internal organs, particularly that of different parts of the alimentary tract showed restoration of close to normal weights.Thus, the weights of the small intestine, jejunum, and ileum in the lectin-pre-treated and 5-FU-injected rats and the non-5-FU-injected control rats were not significantly different.In contrast, in 5-FU-injected rats without prior exposure to PHA the wet- and dry weights of the same intestinal parts were reduced by almost 50% compared to control.The differences seen in the histology sections of the jejunum of rats injected with 5-FU with or without lectin-pre-treatment indicated the protective effect of lectins in stark contrast with the considerable disorganization of the small intestinal tissue in rats that had not been given lectins prior to the 5-FU injection (Figure 2).However, the recombinant forms of the same lectins were quickly degraded in the digestive tract and thus they could no longer protect the gut against the seriously damaging effects of chemotherapy.The use of isolated plant lectins from natural sources as agents to prevent mucositis and the effects of PHA and RPA on the rat intestinal tract and body metabolism are detailed in UK (57) - and World (58) patents.

3.1.3. Use of mistletoe lectins in cancer therapy

The belief in the therapeutic potential of mistletoe preparations in cancer therapy is derived from folk medicine and its effectiveness has till recently been based mainly on anecdotal evidence.More recently there have been some clinical studies with parenterally administered- mistletoe- (59) or the similar *Phoradendron liga (*60) extracts that appeared to back up these.Unfortunately, most of the human clinical studies have been conducted with various mistletoe extracts and not with purified mistletoe lectin(s).Although it is generally agreed that the main active agents in these preparations are the MLs and some of these preparations have even been standardized for their ML content (59, 61, 62) as the preparations are known to contain other biologically active agents this brings some ambiguity into the evaluation of the results.According to the National Cancer Institute (59) the results of the studies can be summarized as follows: extracts of mistletoes have been shown to kill cancer cells and to stimulate the immune system.In Europe but not in the USA a variety of different mistletoe extracts are marketed as injectable prescription drugs.More than 30 clinical trials with mistletoe as a treatment for cancer have been conducted.It has been reported that the survival and

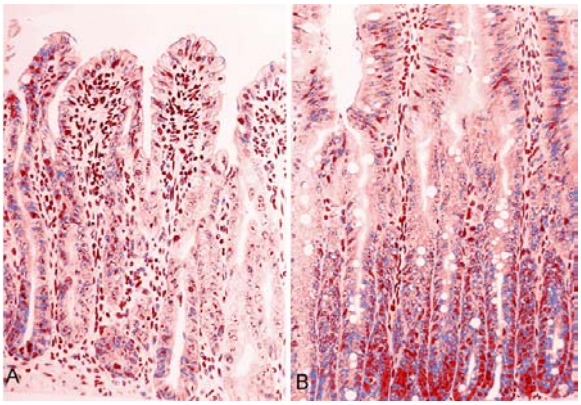

Figure 2. Jejunal section of a 5-fluorouracil (5-FU) injected rat fed on a high-quality diet (a) and a similar section from a rat pre-treated with kidney bean lectin for three days before 5-FU injection (b).Groups of rats were fed high-quality control diet for three days before the start of the experiment.One half of the rats was then intragastrically intubated with 0.9% saline (a) or with 20 mg kidney bean lectin (PHA) (b) daily for three days.After this all rats were *i.p*.injected with 150 mg/kg body weight 5-fluorouracil (5-FU) and then pair-fed on high-quality control diet for four days.The rats were killed, their intestines excised, washed, fixed in paraformaldehyde, sectioned and stained with haematoxylin and eosin.Sections from the rats not receiving a PHA pre-treatment (a) indicated serious disorganization of the epithelial tissue of the jejunum, disruption and considerable shortening of the villi.The epithelial cells on the villus display atrophy with cytoplasmic vacuolation.The crypts are reduced in number and length and contain abnormal mitotic figures.Goblet cells are infrequent on the villi and absent from the crypts.The nuclei of most epithelial cells are enlarged and contain prominent nucleoli.In contrast, the protective effect of PHA-pre-treatment is readily seen in the section (b) from the ordered structure of the crypts.Both the crypts and villi are of normal length (in fact, at the same magnification as in (a) the villi cannot be accommodated on the photomicrographs).Goblet cells are normally distributed throughout both crypts and villi and the transition from crypt to villus is easily identified.

quality of life of the patients have improved but nearly all of the studies had major weaknesses that raised doubts about the reliability of the findings.Thus, at present the use of mistletoe extracts in the USA can only be recommended in well-designed clinical studies.However, it is hoped that some of the ambiguity in the therapeutical use of mistletoes may be avoided by the use of well-characterized purified mistletoe lectins.Unfortunately only few studies had been done with MLs purified from the extracts.Thus, all three MLs (MLI, MLII and MLIII) inhibited melanoma cell proliferation *in vitro*, but of the three different isoforms MLI was found to have the highest cytotoxicity for the cancer cells (63).*Viscum album* agglutinin-I (VAA-I) was shown to possess anti-inflammatory effect, induced apoptosis in activated neutrophils and inhibited lipopolysaccharide-induced neutrophylic inflammation *in vivo* (64, 65), opening the way for future mistletoe therapy.It is hoped that with the recent introduction of recombinant mistletoe lectins one of the main problems in therapy could be overcome, *i.e*.that at least in theory recombinant forms might be more easily obtained in sufficiently large amounts for clinical trials.As a prerequisite for using the recombinant lectin in clinical or even laboratory studies the essential similarity of the natural and recombinant forms of MLs had been demonstrated (66, 67).Studies on the reaction mechanism of the recombinant and the plant-derived MLs on tumour cells *in vitro* and infusion in patients with solid tumours has confirmed their chemical similarity (68, 69).

3.2. Insecticidal effects of lectins

Plant lectins have been found to be one of the most potent naturally occurring insecticidal proteins.It is therefore not surprising that they are extensively used by the biotechnology industry to produce and commercialise lectin-based insecticide-tolerant agricultural crops.Thus, many transgenic plants have been developed using lectin transgenes and the cultivation of genetically engineered (GM) plants is spreading all over the world.Although GM plants at present have no practical biomedical uses it has been suggested that there may be possibilities for abolishing or substantially reducing the allergenicity of plant-based foods by genetic engineering using “antisense” technology.

GM biotechnology (genetic engineering-based biotechnology) makes use of the interaction between insecticidal plant lectins and insects but a full description of these is outside the scope of this review.However, some examples of promising lectins will be briefly mentioned.Thus, some mannose-binding lectins, particularly the *Listera ovata,* LOA, and the snowdrop *(Galanthus nivalis)* bulb agglutinin, GNA, blocked the larval development of the legume pod borer, *Maruca vitrata* (70), while the African yam bean seed lectin inhibited the development of the cowpea weevil but it did not affect the larvae of the legume pod borer (71).A particularly interesting finding was that not only PHA was shown to be lethal to the western tarnished plant bug but also that this was due to the strong binding of the lectin to the cells of the midgut region of the bug, which then became swollen to such an extent that the gut lumen was completely blocked and finally the toxic lectin became endocytosed (72).PHA was also toxic to the tomato moth (*Lacanobia oleracea*) as apparently this lectin was extensively bound to gut glycoproteins of the moth (73).Indeed, in studies of the mechanism of lectin action it was shown, for example, that the binding of the garlic leaf lectin to homopteran pests was correlated with its insecticidal activity (74).Even aphid parasitoids were affected by lectins, such as GNA (75-78).GNA was also found to be effective on stalkborers (79).Wheat germ agglutinin has been shown to have insecticidal effects against the European corn borer because this N-acetylglucosamine-specific lectin does interfere with the formation of the peritrophic membrane in the insect larvae (80).In an important paper conclusive experimental evidence was put forward supporting the idea that the insecticidal activity of lectins is truly dependent on lectin

function because in the presence of the haptenic sugar the insecticidal activity of the lectin was significantly reduced or even abolished (81).Evidence that lectin binding to the digestive system of insects is the main reaction mechanism for the insecticidal effect of lectins in transgenic plants (82, 83) is now generally accepted.The evidence for binding of the various Bt toxins to the digestive system of insects is particularly strong (84-90).The Bt toxin directly and specifically binds glycolipids and this binding is carbohydrate-dependent and relevant for toxin action *in vivo* (91).However, the claimed exclusiveness of the specificity of Bt toxin-binding to the insect gut can no longer be maintained, as there is credible scientific evidence that some Bt toxins will also bind to the gut of mammalian species (92).

The role of lectins and protease inhibitors in plant defence has been reviewed (93).It was also hown that even lectin-like proteins, such as arcelin-1 in bean seeds can have significant insecticidal effects against a number of insects, such as some species of bruchids (94).

3.3. Lectins and bacteria

Lectins are known to directly interact with gut- and other bacteria (95, 96).Their interactions with viruses are however, outwith the scope of this review.Different strains of *Salmonella typhimurium* can be agglutinated by Concanavalin A (Con A) (97).Furthermore, a number of indirect effects of lectins on the composition of the gut flora has been shown.By modifying the glycosylation of epithelial surface cells and thus changing the sites to which bacteria can bind, lectins can induce shifts in the gut bacterial flora, with important nutritional and physiological consequences (9, 98).Modulation of the glycosylation patterns of the intestinal mucosa by the bacterial flora has been described (99).An early example for the lectin-induced change in the bacterial population is the PHA-induced coliform overgrowth in the rat small intestine (100).PHA induces an increase in crypt cell proliferation rate that leads to the flooding of the small intestinal villi with polymannosylated juvenile enterocytes which in turn can form attachment sites to type-1-fimbriated *Escherichia coli*.The mannose-specific binding of *E.coli* and thus the effects of the PHA-induced coliform overgrowth can be partially reversed by GNA, a mannose-specific lectin.This blocking of the attachment site of a bacterium by a lectin with similar sugar binding-specificity is called chemical probiosis (100).

A good example for this type of probiosis is the inhibition of *Salmonella*-binding to Caco-2 cells by peanut agglutinin, PNA because one of the receptors recognised by *Salmonella* is galactosyl-N-acetylgalactosamine and this sugar structure is also recognised by PNA (101).Importantly, GNA given orally significantly reduced the numbers of *Salmonella typhimurium* S986 in the lower part of the small intestine and the large intestine of rats infected with this pathogen and as a result also significantly improved rat growth (97).However, GNA had much less effect on infection with *Salmonella enteritidis* 857 and with Concanavalin A the infection became worse, particularly in the case of *Salmonella typhimurium.* This appears to be a promising line of investigation and many examples, such as the inhibition of Streptococci binding to enamel by plant lectins have been described (102).

3.4. Perspective

It is expected that with our deeper understanding of the interactions of lectins with the gut and other organs of the body the nutritional and biomedical uses of lectins will expand considerably in future, Lectin-based nutriceuticals, diets and possibly even lectin drugs will hopefully be able to make considerable contributions to human/animal health, particularly to the prevention and treatment of diseases, such as cancer, correcting immune deficiencies and hormone imbalances and to optimising the gut flora.It is also hoped that the GM biotechnology industry and its scientists will soon begin to appreciate that the effects of transgenically expressed lectins may not always be beneficial but can also be harmful and thus they can no longer only assume the safety of Bt toxin- or other insecticidal lectin expressing GM crop-based foodstuffs but will have to undertake proper scientifically correct risk analysis before these foods are commercialised.

4. ACKNOWLEDGEMENT

The authors wish to express their appreciation and thanks to Professor Joe Cummins of University of Western Ontario, Canada for the help in selecting, collecting and passing on to us relevant scientific papers on lectin topics that made the writing of this review possible.

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Key Words: Plants, Lectins, Gastrointestinal Tract, Gut Flora, Insecticides, Cancer, Immunity, Medical Applications, Biotechnology, Review

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