



Research Article

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Exhaustive Overview of Dietary Plant Lectins: Prospective Importance in the Mediterranean Diet

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To Cite This Article: Ian F Pryme, Truls M Aarra. Exhaustive Overview of Dietary Plant Lectins: Prospective Importance in the Mediterranean Diet. *Am J Biomed Sci & Res.* 2021 - 13(4). *AJBSR.MS.ID.001883*. DOI: [10.34297/AJBSR.2021.13.001883](https://doi.org/10.34297/AJBSR.2021.13.001883).

Received: 📅 July 02, 2021; Published: 📅 July 12, 2021

Abstract

Stillmark reported in 1888 that castor bean extracts were able to agglutinate red blood cells from different species [1]. The seed extracts were found to contain haemagglutinating proteins, defined as agglutinins. Haemagglutinins are now known as lectins, a term proposed many years ago. Lectins are a very heterogeneous group of proteins of non-immune origin and have gone through several definition steps resulting in lesser strictness over the years. Some years ago, Van Damme defined lectins as: "carbohydrate-binding proteins possessing at least one non-catalytic domain, which bind reversibly to a specific mono- or oligosaccharide" [2]. The continuous discovery of new and diverse lectins with similarities found in several different classes of proteins seems to call for even less strict definitions in the future. Maybe the most accurate lectin definition would simply be: "proteins that specifically bind or cross-bind carbohydrates". Lectins are becoming more and more interesting as components of our diet, and it is interesting to note that in the U.S. News and World Report of 2020 the Mediterranean diet has been named as the best overall healthy diet [3]. The diet is well-known for its high content of vegetables, fruits and nuts and whole grains. This review examines our current knowledge of its importance for the Mediterranean diet.

Keywords: Lectins, Beneficial effects on health, Mediterranean diet, Cancer

Introduction

Lectins are widespread in the plant kingdom, occurring in seeds and all kinds of vegetative tissues, and often take part in the plants defence system against predators such as insects, worms etc [4]. To prevent the plant being fed on, lectins are not very tasteful, and severely interfere with digestive processes in insects and worms. Lectins and many other low molecular weight components in foodstuffs are thus called antinutrients because they often have a negative impact on the nutritional value of diets containing them. As biologically active proteins, lectins are very seldom harmful. Some are able to modify and sometimes improve gut function and body metabolism. They can also alter health status as well [5]. Animal lectins, on the other hand, are usually secreted from the cells where they may participate in cell-cell-interactions, recognition of immune defence systems, immunoregulation and prohibition of autoimmunity [6-8]. Due to the homology between plant and animal lectins, it is likely that the dietary plant lectins to

some extent can mimic and amplify the effects normally exerted by their lectin counterparts produced by the animals themselves.

A large number of plant, animal and microbe lectins have now been isolated [9-17]. Lectins are widespread in the plant kingdom (fruits, nuts, vegetables), occurring in seeds and all kinds of vegetative tissues, and often take part in the plants defence system against predators such as insects, worms etc. In many cases lectins severely interfere with digestive processes in such predators. Lectins and many other low molecular weight components in foodstuffs are thus called antinutrients because they often have a negative impact on the nutritional value of diets containing them. However, most of the antinutritional effects can be eliminated or substantially reduced with proper storage, heat treatment, soaking, and germination. As biologically active proteins some are able to modify and sometimes improve gut function and body metabolism, and thus can also improve health status.

The number of lectins found in various parts of plants has now become extensive and in order to bring the reader up-to-date Table 1 [17-92] contains an overview of lectins in vegetables, fruits, cereals, seeds and nuts, and herbs and spices. As we can see more than 100 dietary vegetables contain lectins and the number of fruits is over 55. The Health Authorities in Western society have advised its members to adopt the principle of "5 a day", that is one should

include in the daily diet five portions of vegetables, fruits, cereals and nuts etc., amounting to about 400g per day [3]. In Greece, Italy, Spain and Turkey where the Mediterranean diet is used then the risk of suffering from heart disease is reduced. It is thus evident that to ensure long-term good health the diet needs to have an adequate content of plant lectins.

Table 1: Lectins in Vegetables, Fruits, Cereals, Seeds and Nuts, Flowers, Herbs and Spices.

Vegetables			
Adzuki bean	<i>Vigna angularis</i>	[17]	Grant et al (1983)
Alfalfa	<i>Medicago sativum</i>	[18]	Zhang et al (2008)
Alpine split pea	<i>Phaseolus sativum</i>	[19]	Boyd & Reguera (1949)
Angled luffa	<i>Luffa acutangula</i>	[20]	Srinivas Naik et al (2014)
Asparagus	<i>Asparagus officinalis</i>	[21]	Hossaini (1968)
Asparagus pea	<i>Lotus tetragonolobus - L</i>	[22]	Yariv et al (1967)
Beet	<i>Beta vulgaris</i>	[18]	Zhang et al (2008)
Black turtle bean	<i>Phaseolus vulgaris var</i>	[23]	Shudong He et al (2015)
Blackeyed pea	<i>Vigna sinensis</i>	[17]	Grant et al (1983)
Brazilian Jack Bean	<i>Canavalia brasiliensis</i>	[14]	González de Mejía & Prisecaru (2005)
Brittle wax bush bean	<i>Phaseolus vulgaris, var. humilis</i>	[19]	Boyd & Reguera (1949)
Broad bean	<i>Vicia faba</i>	[14]	González de Mejía & Prisecaru (2005)
Brussel sprouts	<i>Brassica oleracea</i>	[24]	Huang Deqi et al (1992)
Butter bean	<i>Phaseolus limensis</i>	[19]	Boyd & Reguera (1949)
Cargen cress	<i>Lepidium sativum</i>	[18]	Zhang et al (2008)
Carrot	<i>Daucus carota</i>	[25]	Su & Tung (1989)
Cauliflower	<i>Brassica oleracea var botrytis</i>	[20]	Srinivas Naik et al (2014)
Celery	<i>Apium graveolens</i>	[21]	Hossaini (1968)
Ceylon spinach	<i>Basella rubra</i>	[22]	Srinivas Naik et al (2014)
Celery	<i>Apium graveolens</i>	[26]	Davidson & Stewart (2004)
Chickpea	<i>Cicer arietinum</i>	[19]	Boyd & Reguera (1949)
Chilli	<i>Capsicum annum</i>	[25]	Su & Tung (1989)
Chinese cabbage	<i>Brassica rapa</i>	[25]	Su & Tung (1989)
Chinese chive	<i>Allium tuberosum</i>	[27]	Oii et al (2002)
Chinese spinach	<i>Amaranthus tricolor</i>	[19]	Boyd & Reguera (1949)
Climbing French bean	<i>Phaseolus vulgaris sp.</i>	[14]	González de Mejía & Prisecaru (2005)
Cluster bean	<i>Cyamopsis tetragonoloba</i>	[20]	Srinivas Naik et al (2014)
Cowpea	<i>Vigna unguiculata</i>	[28]	Roberson & Strength (1983)
Crow garlic	<i>Allium vineale</i>	[29]	Van Damme et al (1991)
Cucumber	<i>Cucumis sativus</i>	[30]	Allen (1979)
Dwarf bean	<i>Phaseolus vulgaris, var.</i>	[19]	Boyd & Reguera (1949)
Dwarf flowering onions	<i>Allium moly</i>	[29]	Van Damme et al (1991)
Dwarf sugar peas	<i>Pisum sativum, var. humile</i>	[19]	Boyd & Reguera (1949)
Early Alaska peas	<i>Pisum sativum, var. humile</i>	[19]	Boyd & Reguera (1949)
Edible mushroom	<i>Agaricus bisporus</i>	[14]	González de Mejía & Prisecaru (2005)
Fava bean	<i>Vicia faba</i>	[31]	Hemperly et al (1979)
Field bean	<i>Dolichos lablab</i>	[32]	Manage et al (1972)

Field mushroom	<i>Agaricus campestris</i>	[19]	Boyd & Reguera (1949)
French bean	<i>Phaseolus vulgaris sp.</i>	[19]	Boyd & Reguera (1949)
Garden pea	<i>Pisum sativum L.</i>	[17]	Grant et al (1983)
Garlic	<i>Allium sativum L.</i>	[25]	Su & Tung (1989)
Grass pea	<i>Lathyrus sativa</i>	[33]	Purkait & Koley (2019)
Green pea	<i>Phaseolus sativum</i>	[10]	Nachbar & Oppenheim (1980)
Horse gram bean	<i>Macrotyloma uniflorum</i>	[20]	Srinivas Naik et al (2014)
Hyacinth bean	<i>Lab-lab purpureus</i>	[20]	Srinivas Naik et al (2014)
Jack bean	<i>Canavalia ensiformis</i>	[10]	Nachbar & Oppenheim (1980)
Jap. red sword bean	<i>Canavalia gladiata</i>	[35]	Une et al (2018)
Jerusalem artichoke	<i>Helianthus tuberosus L.</i>	[14]	González de Mejía & Prisecaru (2005)
Kidney bean	<i>Phaseolus vulgaris L.</i>	[14]	González de Mejía & Prisecaru (2005)
Knife bean	<i>Canavalia gladiata</i>	[36]	Wong & Ng (2005)
Lablab bean	<i>Dolichos lablab</i>	[19]	Boyd & Reguera (1949)
Laxtons progress (pea)	<i>Pisum sativum var. humile</i>	[19]	Boyd & Reguera (1949)
Leaf beat/chard	<i>Beta vulgaris ssp. cicla</i>	[26]	Davidson & Stewart (2004)
Leek	<i>Allium porrum</i>	[29]	Van Damme et al (1991)
Lentil	<i>Lens esculenta</i>	[14]	González de Mejía & Prisecaru (2005)
Lima bean	<i>Phaseolus coccineus</i>	[19]	Boyd & Reguera (1949)
Lima bean-Alpine	<i>P. limensis</i>	[14]	Boyd & Reguera (1949)
Lentil	<i>Lens culinaris</i>	[14]	González de Mejía & Prisecaru (2005)
Lentil sprouts	<i>Lens esculenta</i>	[10]	Nachbar & Oppenheim (1980)
Lettuce	<i>Lactuca sativa</i>	[25]	Su & Tung (1989)
Lima bean	<i>Phaseolus lunatus</i>	[33]	Purkait & Koley (2019)
Lupin beans	<i>Lupinus hybridus</i>	[37]	Renkonen (1948)
Marrow	<i>Curcubita pepa</i>	[30]	Allen (1979)
Mat/moth bean	<i>Vigna aconitifolia</i>	[33]	Purkait & Koley (2019)
Mung bean	<i>Phaseolus mungo</i>	[17]	Grant et al (1983)
Mung bean sprouts	<i>Phaseolus mungo</i>	[38]	Hankins & Shannon (1978)
Narrowleaf lupin beans	<i>Lupinus angustifolius</i>	[37]	Renkonen (1948)
Navy (white) bean	<i>Vigna radiata</i>	[37]	Renkonen (1948)
Okra	<i>Abelmoschus esculentus</i>	[39]	Guruvayoorappan et al (2015)
Onion	<i>Allium cepa</i>	[25]	Su & Tung (1989)
Parsley	<i>Petroselinum hortense</i>	[18]	Zhang et al (2008)
Pea beans	<i>Phaseolus sp.</i>	[19]	Boyd & Reguera (1949)
Pigeon pea	<i>Cajanus cajan</i>	[17]	Grant et al (1983)
Pinto bean	<i>Phaseolus vulgaris sp.</i>	[19]	Boyd & Reguera (1949)
Pole bean	<i>Phaseolus vulgaris sp.</i>	[19]	Boyd & Reguera (1949)
Potato	<i>Solanum tuberosum</i>	[10]	Nachbar & Oppenheim (1980)
Prickly lettuce	<i>Lactuca sasole</i>	[87]	Yen et al (1980)
Profi pea	<i>Pisum arvense</i>	[14]	González de Mejía & Prisecaru (2005)
Radish	<i>Raphanus sativus</i>	[40]	Tsumuraya et al (1988)
Ramsons	<i>Allium ursinum</i>	[29]	Van Damme et al (1991)
Runner bean	<i>Phaseolus coccineus</i>	[19]	Boyd & Reguera (1949)
Rutabaga/swede	<i>Brassica napobrassica</i>	[21]	Hossaini (1968)
Scarlet gourd	<i>Coccinia indica</i>	[41]	Sanadi & Surolia (1994)
Shallot	<i>Allium ascalonicum</i>	[29]	Van Damme et al (1991)

Siberian pea tree	<i>Caragana arborescens</i>	[42]	Doyle et al (1982)
Snap pea	<i>Pisum sativum var. macrocarpon</i>	[39]	Guruvayoorappan et al (2015)
Soybean	<i>Glycine max</i>	[14]	González de Mejía & Prisecaru (2005)
Soy bean sprouts	<i>Glycine Max</i>	[10]	Nachbar & Oppenheim (1980)
Speckled bean	<i>Phaseolus sp.</i>	[19]	Boyd & Reguera (1949)
Spinach	<i>Spinacia oleracea</i>	[20]	Srinivas Naik et al (2014)
Spiny gourd	<i>Momordica dioica</i>	[43]	Dimple et al (2018)
String bean	<i>Phaseolus vulgaris</i>	[10]	Nachbar & Oppenheim (1980)
Sutton's runner bean	<i>Phaseolus coccineus</i>	[19]	Boyd & Reguera (1949)
Sweet pepper/paprika	<i>Capsicum annum</i>	[43]	Krüppe (1956).
Sweet pea	<i>Lathyrus odoratus</i>	[44]	Kolberg & Sletten (1978)
Sweet potato	<i>Ipomoea batatas</i>	[20]	Srinivas Naik et al (2014)
Swiss chard	<i>Beta vulgaris</i>	[46]	Gold & Balding (1975)
Taro	<i>Colocasia esculenta</i>	[47]	Pereira et al (2014)
Tepary bean	<i>Phaseolus acutifolius</i>	[48]	Ferriz-Martinez et al (2015)
Tonka beans	<i>Dipteryx odorata</i>	[37]	Renkonen (1948)
Tomato	<i>Lycopersicon esculentum</i>	[10]	Nachbar & Oppenheim (1980)
Turnip/beet	<i>Brassica campestris rapa</i>	[21]	Hossaini (1968)
Wax pod bush bean	<i>P.vulgaris, var. humilis</i>	[19]	Boyd & Reguera (1949)
Wild celery	<i>Angelica archangelica</i>	[2]	Van Damme et al (1997)
Wild soybean	<i>Glycine soja</i>	[37]	Renkonen (1948)
Winged bean	<i>Psophocarpus tetragonobolus</i>	[37]	Renkonen (1948)
Vegetable marrow	<i>Curcubita pepo</i>	[30]	Allen (1979)
Zucchini	<i>Curcubita pepo</i>	[30]	Allen (1979)
Fruits			
American plum	<i>Prunus americana</i>	[19]	Boyd & Reguera (1949)
Apple	<i>Malus domestica</i>	[25]	Su & Tungl (1989)
Apricot	<i>Prunus armeniaca</i>	[20]	Srinivas Naik et al (2014)
Artocarpus	<i>Artocarpus tonkinensis</i>	[49]	Blasco et al (1996)
Banana	<i>Musa acuminata L.</i>	[25]	Su & Tung (1989)
Banana	<i>Musa paradisiac</i>	[50]	Koshte et al (1990)
Bitter melon	<i>Momordica charantia</i>	[20]	Srinivas Naik et al (2014)
Blackberry	<i>Rubus fruticosus</i>	[51]	Liénart et al (1991)
Breadfruit	<i>Artocarpus altilis</i>	[52]	Pineau et al (1990)
Camaratu bean	<i>Cratylia mollis</i>	[53]	Souza et al (2001)
Cantaloupe	<i>Cucumis melo cantalupensis</i>	[18]	Zhang et al (2008)
Cempedak	<i>Artocarpus chameden</i>	[49]	Blasco et al (1996)
Chempedak	<i>Artocarpus integer</i>	[49]	Blasco et al (1996)
Cherry	<i>Prunus avium bigarreaus</i>	[18]	Zhang et al (2008)
Currant	<i>Ribes rubrum</i>	[18]	Zhang et al (2008)
Date	<i>Phoenix dactylifera</i>	[20]	Srinivas Naik et al (2014)
Elderberry	<i>Sambucus nigra</i>	[14]	González de Mejía & Prisecaru (2005)
Ginger	<i>Zingibar officinale</i>	[25]	Su & Tung (1989)
Grape	<i>Vitis vinifera</i>	[20]	Srinivas Naik et al (2014)
Grapefruit	<i>Citrus medica</i>	[18]	Zhang et al (2008)
Ground elder	<i>Aegopodium podagraria</i>	[6]	Peumans & Van Damme (1985)
Guava	<i>Psidium guava</i>	[54]	Bhat et al (2018)

Jackfruit	<i>Artocarpus integrifolia</i>	[55]	Kabir & Daar (1994)
Jambolan	<i>Syzygium jambolanum</i>	[20]	Srinivas Naik et al (2014)
Japanese red elder	<i>Sambucus sieboldiana</i>	[56]	Tazaki & Shibuya (1989)
Jujube red date	<i>Zizyphus jujuba</i>	[20]	Srinivas Naik et al (2014)
Kiwi	<i>Actinidia deliciosa</i>	[25]	Su & Tung (1989)
Lemon	<i>Citrus medica</i>	[25]	Su & Tung (1989)
Lime	<i>Citrus aurantifolia</i>	[57]	Helleland & Pryme (2012)
Malabar plum	<i>Syzygium cumnii</i>	[20]	Srinivas Naik et al (2014)
Mango	<i>Mangifera indica</i>	[20]	Srinivas Naik et al (2014)
Melon	<i>Curumis melo</i>	[25]	Su & Tung (1989)
Monkey fruit	<i>Artocarpus lacucha</i>	[58]	Chowdhury et al (1987)
Mulberry	<i>Morus alba L.</i>	[59]	Yeasmin et al (2001)
Mungbean sprouts	<i>Phaseolus mungum</i>	[18]	Zhang et al (2008)
Orange	<i>Citrus sinensis</i>	[25]	Su & Tung (1989)
Papaya	<i>Carica papaya</i>	[60]	Wang et al (2011)
Passion fruit	<i>Passiflora edulis</i>	[25]	Su & Tung (1989)
Plum	<i>Prunus domestica</i>	[20]	Srinivas Naik et al (2014)
Peacock ginger	<i>Kaempferia rotunda</i>	[61]	Kabir & Reza (2014)
Pineapple	<i>Ananas comosus</i>	[25]	Su & Tung (1989)
Pitanga	<i>Eugenia uniflora</i>	[62]	Oliveira et al (2008)
Plum	<i>Spontia vulgaris</i>	[25]	Su & Tung (1989)
Pomegranate	<i>Punica granatum</i>	[18]	Zhang et al (2008)
Pomerans	<i>Citrus aurantium</i>	[44]	Kruppe (1956)
Pumpkin	<i>Curcubita maxima</i>	[63]	Smith et al (1987)
Quince	<i>Cydonia vulgaris</i>	[64]	Coutino-Rodriguez et al (2001)
Raspberry	<i>Rubrus idaeus</i>	[18]	Zhang et al (2008)
Rhubarb	<i>Rheum rhapontium</i>	[18]	Zhang et al (2008)
Snake gourd	<i>Trichosanthes cucumerina anguina</i>	[20]	Srinivas Naik et al (2014)
Squash	<i>Curcubita maxima</i>	[20]	Srinivas Naik et al (2014)
Strawberry	<i>Fragaria vesca</i>	[18]	Zhang et al (2008)
Sugar beet	<i>Beta vulgaris ssp. saccharifera</i>	[65]	Vyskrebentseva & Borisova (1966)
Summer grape	<i>Vitis aestivalis</i>	[19]	Boyd & Reguera (1949)
Tamarind	<i>Tamarindus indica</i>	[54]	Bhat et al (2018)
Tejocote	<i>Crataegus mexicanus</i>	[54]	Bhat et al (2018)
Water melon	<i>Citrullus vulgaris</i>	[18]	Zhang et al (2008)
Wheat germ	<i>Secale cereale</i>	[66]	Peumans et al (1982)
White mulberry	<i>Morus alba</i>	[20]	Srinivas Naik et al (2014)
Zucchini	<i>Cucubrita pepo</i>	[18]	Zhang et al (2008)
Cereals			
Barley	<i>Hordeum vulgare</i>	[33]	Purkait & Koley (2019)
Corn/Maize	<i>Zea mays</i>	[67]	Markov & Khavkin (1982)
Oats	<i>Avena sativa</i>	[68]	Langston-Unkefer & Gade (1984)
Rice	<i>Oryza sativa L.</i>	[18]	Zhang et al (2008)
Rye	<i>Secale cereale</i>	[66]	Peumans et al (1982)
Sorghum	<i>Sorghum bicolor</i>	[33]	Purkait & Koley (2019)
Triticale	<i>Triticale spp.</i>	[69]	Hariharan & Rao (1978)
Wheat	<i>Triticum aestivum L.</i>	[14]	González de Mejía & Prisecaru (2005)

Wheat germ	<i>Tritium vulgaris</i>	[70]	Hamid & Masood (2009)
Seeds and nuts			
Amaranth	<i>Amaranthus caudatus</i>	[19]	Boyd & Reguera (1949)
Baru almonds	<i>Dipteryx alata Vog.</i>	[71]	Fraguas et al (2014)
Caraway seeds	<i>Carum carvi</i>	[18]	Zhang et al (2008)
Caraway	<i>Trachyspermum ammi</i>	[33]	Purkait & Koley (2019)
Coconut	<i>Cocos nucifera</i>	[18]	Zhang et al (2008)
Coral vine	<i>Antigonon leptopus</i>	[2]	Van Damme et al (1997)
Griffonia seeds	<i>Griffonia simplicifolia</i>	[14]	González de Mejía & Prisecaru (2005)
Hazelnut	<i>Corylus avellana</i>	[70]	Hamid & Masood (2009)
Hog-peanut	<i>Amphicarpaea bracteata</i>	[42]	Doyle et al (1982)
Lebbeck	<i>Albizia lebbeck</i>	[72]	Adamude et al (2020)
Mimosa tree seeds	<i>Albizia julibrissin</i>	[42]	Doyle et al (1982)
Okra	<i>Abelmoschus esculentus</i>	[73]	Soares et al (2012)
Peanut/ground nut	<i>Arachis hypogea</i>	[74]	Lotan et al (1975)
Pinhao	<i>Aurocaria brasiliensis</i>	[75]	Datta et al (1991)
Pistacio nut	<i>Pistacia vera</i>	[20]	Srinivas Naik et al (2014)
Red lucky seed	<i>Adenantha pavonina</i>	[76]	Prakashkumar et al (1997)
Sesame seeds	<i>Sesamum indicum</i>	[33]	Purkait & Koley (2019)
Solomons seeds	<i>Polygonatum cyrtonema</i>	[77]	Liu et al (2009)
Sunflower seeds	<i>Helianthus annuus</i>	[18]	Zhang et al (2008)
Walnut	<i>Juglans regia</i>	[18]	Zhang et al (2008)
Flowers, herbs and spices			
Alisma	<i>Alisma orientalis</i>	[79]	Shao et al (2011)
Allspice	<i>Pimenta officinalis</i>	[18]	Zhang et al (2008)
Amaryllis	<i>Hippeastrum hybrid</i>	[78]	Sharma et al (1996)
Arum	<i>Arum maculatum</i>	[78]	Sharma et al (1996)
Astragalus	<i>Astragalus mongholicus</i>	[80]	Yan et al (2005)
Black mustard	<i>Brassica niagra</i>	[33]	Purkait & Foley (2019)
Black pepper	<i>Piper nigrum</i>	[20]	Srinivas Naik et al (2014)
Black tumeric	<i>Curcuma amarissima Roscoe</i>	[82]	Kheeree et al (2010)
Camels foot tree	<i>Bauhinia purpurea</i>	[42]	Doyle et al (1982)
Candelabra aloe	<i>Aloe arborescens</i>	[42]	Doyle et al (1982)
Celandine	<i>Chelidonium majus</i>	[14]	González de Mejía & Prisecaru (2005)
Chicory	<i>Chichorium intybus</i>	[46]	Gold & Balding (1975)
Cocoa	<i>Theobroma cacao</i>	[18]	Zhang et al (2008)
Coffee	<i>Coffea arabica</i>	[18]	Zhang et al (2008)
Common broom	<i>Sarothamnus scoparius</i>	[84]	Gurtler (1978)
Coriander	<i>Corandrum sativum</i>	[33]	Purkait & Koley (2019)
Desert false indigo	<i>Amorpha fruticose</i>	[19]	Boyd & Reguera (1949)
Fenugreek	<i>Trigonella coerulea</i>	[37]	Renkonen (1949)
Flame-of-the-forest	<i>Butea monosperma</i>	[76]	Prakashkumar et al (1997)
Gorse	<i>Ulex europaeus</i>	[86]	Horejsi & Kocourek (1974)
Greater celendine	<i>Chelidonium majus</i>	[78]	Sharma et al (1996)
Indian cress	<i>Tropaeolum majus</i>	[19]	Boyd & Reguera (1949)
Jack-in-the-pulpit	<i>Arisaema tryphyllum</i>	[88]	Boyd et al (1961)

Japanese pagoda	<i>Styphnolobum japonicum</i>	[90]	Hankins et al (1988)
Marjoram	<i>Labiaca organum</i>	[18]	Zhang et al (2008)
Mistletoe	<i>Viscum album</i>	[89]	Franz et al (1981)
Nutmeg	<i>Myristica fragrans</i>	[70]	Hamid & Masood (2009)
Peppermint	<i>Menta piperita</i>	[70]	Hamid & Masood (2009)
Plantain	<i>Musa sp.</i>	[14]	González de Mejía & Prisecaru (2005)
Rattlepods	<i>Crotolaria sp.</i>	[35]	Khanne & Sehajpal (1980)
Red clover	<i>Trifolium pratense</i>	[37]	Renkonen (1948)
Sapota	<i>Achras zapota</i>	[20]	Srinivas Naik et al (2014)
Scorpion's tails	<i>Scorpiurus vermiculatus</i>	[37]	Renkonen (1948)
Sickle senna	<i>Cassia tora</i>	[91]	Grant et al (1991)
Snakes beard	<i>Ophiopogon japonicus</i>	[92]	Liu et al (2009)
Snapdragon	<i>Antirrhinum majus</i>	[2]	Van Damme et al (1971)
Snowdrop	<i>Galanthus nivalis</i>	[78]	Sharma et al (1996)
Sow thistle	<i>Sonchus oleraceus</i>	[35]	Khanne & Sehajpal (1980)
Stinging nettle	<i>Urtica dioica</i>	[14]	González de Mejía & Prisecaru (2005)
Tian ma	<i>Gastrodia elata</i>	[92]	Liu et al (2002)
Tea	<i>Hibiscus rosa sinensis</i>	[35]	Khanne & Sehajpal (1980)
Turmeric	<i>Curcuma domestica</i>	[20]	Srinivas Naik et al (2014)
White/black tea	<i>Camellia sinensis</i>	[20]	Srinivas Naik et al (2014)
Yellow sweet clover	<i>Melilotus indicus</i>	[37]	Renkonen (1948)
Yellow bauhinia	<i>Bauhinia tomentosa</i>	[37]	Renkonen (1948)

National campaigns encouraging people to eat "5 a day", have not been particularly successful. In Scotland, for example, daily consumption between 1993 and 2000 only increased from 190g to 200g. Since there is considerable evidence that consumption of sufficient amounts of fruit and vegetables has an impact on preventing many chronic diseases (heart disease, stroke, several forms of cancer, for example [93], these results are certainly disheartening.

What Happens to Dietary Lectins?

Sharma *et al* [78] demonstrated that a series of plant lectins can bind to receptors on the surfaces of human intestinal cells (biopsy material). Following binding to appropriate receptors, lectins can then propagate release of intracellular second messenger molecules. Although lectin binding is most extensive in the small intestine, binding can occur throughout the entire GIT from the oral cavity to the distal colon. Lectin-binding studies on human small intestine biopsy material, showed that a series of plant lectins can bind to receptors on the surfaces of different types of cells found in Peyer's patches [78]. From Aricigil and Pryme [12] (see Table 1.3) we see that the overall frequency of binding of 27 selected lectins to Follicle-associated epithelium (FAE), Villus epithelium (VE) and Gut-associated lymphoid tissue (GALT) was 59 %, 70 % and 44 %, respectively.

It is thus evident that the three areas bind lectins to various degrees. The different cell types in the three areas of Peyer's patches also demonstrate varying levels of binding specificity. For example, in GALT lymphocytes only bound 11 % of the lectins while macrophages bound 41 %. A further level of specificity is illustrated by the fact that in FAE only 5 of the 27 lectins were shown to bind to all cell types, in VE 4/27 and in GALT only two lectins were seen to bind to both lymphocytes and macrophages. These observations illustrate the complex pattern of binding of lectins to the various cell types found in Peyer's patches.

The complexity of binding is further illustrated by the results shown by Sharma *et al* [78]. Three lectins all with the same binding specificity for D-GalNac exhibit different staining patterns in binding studies performed on different cell types in three areas of human Peyer's patches. The Bryonia dioica (BDA) lectin has a very high affinity for binding to macrophages in GALT. ML binds strongly to M-cells and enterocytes of FAE while SNA binds with high intensity to goblet cells of VE and macrophages in GALT. The biological significance of these observations is currently unknown, though it is tempting to speculate, that lectins that have the property of binding to different cell types associated with well-defined areas of Peyer's patches will initiate separate, and perhaps specific biological responses.

Etzler and Branstrator [94] studied sections of small intestine from adult male rats. These were examined by fluorescence microscopy after treatment with fluorescein isothiocyanate-labeled lectins from *Dolichos biflorus*, *Lotus tetragonolobus*, *Ricinus communis*, and *Triticum vulgare* (wheat germ). The latter three lectins reacted with the microvillar portion of the epithelial cells lining the crypts and villi in sections of intestine adjacent to the pylorus. This pattern of reactivity was sharply altered along the first 15 cm of intestine so that in sections distal to this point the luminal surfaces of only those epithelial cells in the crypts and at the base of the villi reacted with the *L. tetragonolobus* and *R. communis* lectins, whereas the wheat germ lectin reacted with the surfaces of cells lining the villi. In sections from the distal end of the small intestine, all three lectins reacted with the surfaces of cells only at the base of the villi and in the crypts.

These results show a difference in surface components in cells at various portions on the villi, and the dependence of these differences on the region of intestine. The *D. biflorus* lectin reacted with approximately 25% of the goblet cells at each level of intestine studied. Whereas the reactivities of the goblet cells with the other three lectins were dependent upon the region of intestine.

Most lectins, in line with all other proteins, are inactivated under conditions that lead to irreversible protein denaturation, for example heat, and thereby lose their biological activity. However, different plant lectins exhibit varying levels of heat stability, such that many, but not all, are inactivated as a result of cooking, frying, grilling etc. Raw vegetables though, and fruit and nuts, will thus have a high content of biologically active lectins.

This unique group of proteins have potent biological activity following their ingestion. Several lectins, for example, have been found to possess anticancer properties both *in vitro*, *in vivo*, and in human case studies [95-100]. Some lectins can preferentially bind to cancer cell membranes or their receptors, causing cytotoxicity upon internalization and activation, resulting in apoptosis and cessation of tumour growth [101-102].

Lectins are able to modify the cell cycle by inducing non-apoptotic G1-phase accumulation mechanisms, G2/M phase cell cycle arrest and apoptosis, and can activate the caspase cascade. They can also down-regulate telomerase activity and result in an inhibition of angiogenesis [101]. Ingestion of specific lectins can lead to a sequestration of the available body pool of polyamines, resulting in reduced cancer cell growth. Many lectins have been shown to stimulate the immune system by altering the production of various interleukins. This may indeed be an extremely important property of the dietary lectins since they are able to prime the immune system, thus keeping it activated.

It would seem likely that NK cells have a similar role in the immunologic surveillance against cancer in humans and that plant lectins here play a vital role [102]. There is, therefore, a strong indication of the importance of keeping the number of activated NK cells in the blood within normal limits.

Many lectins taken orally are resistant to low pH and proteolytic breakdown due to their carbohydrate shell and complex structure. They thus remain fully active during their passage through the entire alimentary canal [103]. The surface of the mammalian gut is highly glycosylated, and the epithelium is covered by glycolipids and glycoproteins. Through their saccharide binding, lectins bind to epithelial membrane glycoproteins, including receptors of hormones, growth factors and cytokines, transport proteins and brush-border membrane enzymes, glycolipids, gangliosides and secreted mucins [103,104]. Although lectin binding is most extensive in the small intestine, similar binding does occur throughout the entire digestive system from the oral cavity to the distal colon. The lectin can send messages into the cell via second messengers or by the lectin itself entering the cell by endocytosis.

The major effects mediated by lectin binding in the digestive tract are: (a) hyperplasia, increase in crypt cell production rate (b) overstimulation of secretory cells and exhaustion of their secretory capacity, (c) replacement of appropriate endogenous ligands bound to their receptors, and (d) immune stimulation. Both (a) hyperplasia and (d) immune stimulation are indeed today interesting aspects in cancer research.

Some plant lectins have a high level of glycosylation and others are characterised by having a very tight globular structure. These molecules can therefore be extremely resistant to digestive processes and are therefore not completely degraded following exposure to acid and proteolytic enzymes in the GIT. Their biological activity thus being to a large extent retained during intestinal passage. For example, >90% of phytohaemagglutinin (PHA) and >60 of *Sambucus nigra* (SNA) lectins in kidney bean and elderberry, respectively, were recovered in an active form [105]. Very many lectins can thus remain fully biologically and immunogenically active during their passage through the entire alimentary canal [78]. Those lectins that survive will thus be able to bind to cells present in the intestine that bear appropriate receptors [2,105]. The mammalian gut surface is highly glycosylated and the epithelium is covered by numerous glycolipids and glycoproteins. Because of their affinity for saccharides, lectins bind to epithelial membrane glycoproteins, including receptors for hormones, growth factors and cytokines, transport proteins and brush-border membrane enzymes, glycolipids, gangliosides and secreted mucins [78].

As seen in Aricigil and Pryme [12, see Figure 1.1] a lectin, following binding to the cell surface, can send information into the

cell's interior via second messengers and instigate an intracellular response. This is often manifested in the form of a modulation of gene expression and it has been envisaged that biologically active molecules such as cytokines, growth factors, hormones or enzymes may be produced, as suggested by *Bardocz et al* [105]. These molecules may be released from the cell and then result in a systemic effect. On the other hand active products may be transported to neighbouring cells inducing some form of local stimulation. A lectin, though, may enter itself the cell through endocytosis and then cause a direct intracellular effect.

The GIT, through its entire length, has various levels of glycosylation. Specific lectin binding can be therefore very different in the stomach, small intestine, and large intestine [78, 103]. Different lectins can also bind to the same cell surface and these can therefore exert a synergistic response. In Figure 1.1, Aricigil and Pryme [12], we can see that two different lectins (labeled A and B) may bind to their respective receptors on the surface of the same cell. This would of course be dependent on the two lectins being present in the intestine at the same time, thus illustrating the importance of a multicomponent diet. At the present time our knowledge concerning the possible simultaneous involvement of a number of dietary lectins in causing a positive biological response is virtually non-existent.

A lectin can either stimulate a receptor in the same manner as an endogenous ligand, or either strengthen, weaken or even inhibit the signal initiated by the primary ligand-receptor interaction. It is likely that this occurs as a result of the lectin-bound receptor complex releasing second messengers that can in turn modulate gene expression. Newly synthesised molecules are able to reach appropriate targets (extracellular or intracellular) and there induce different forms of biological response e.g. immuno-stimulation.

Oral Immunogenicity

The function of the gut associated lymphoid tissue is to absorb minute samples of oral antigens via Peyer's patches M-cells and activate the gut immune system. As lectins are able to bind to M-cells [106], their endocytosis is more extensive, which makes them more powerful immunogens than other antigens. Lectins influence the immune system by evoking local and systemic immune responses and sometimes they can induce strong allergenic reactions [107-109]. Mitogenic lectins are inducers of lymphocyte proliferation. Several components of the immune system, such as mast cells, basophils, eosinophils and others produce or release cytokines and chemokines when exposed to appropriate lectins.

The Effect of Plant Lectins in Animal Model Systems and Observations Made in Humans

Research performed on plant lectins has been mainly performed on laboratory animals. It is likely that many of the interesting findings cannot be directly transferred to humans. This is a direct result of the conditions prevailing during the experiments; firstly, much larger doses have been administered than would be realistic for humans to consume, secondly, the method of application e.g. by intragastric intubation or subcutaneous injection, is often not at all relevant in the "normal" human situation, and thirdly, in animal experiments the effects of a single given lectin have been typically studied and this is atypical for our human lifestyle where, on a balanced diet of vegetables, fruit and nuts, a series of lectins would be ingested, often during the same meal. In Table 2 we see the approximate amounts of lectin present in common foodstuffs. It is apparent that the amounts vary considerably from the kidney bean (<500mg/50g) to the tomato (<0.05mg/50g). These values, however, are dependent on the nature of the form of preparation of the foodstuff prior to its consumption.

Table 2: Approximate amounts of lectin in non-cooked common foods.

Kidney bean	<i>Phaseolus vulgaris</i>	<500mg/50g
Taro	<i>Colocasia esculenta</i>	<250mg/50g
Peanut	<i>Arachis hypogea</i>	<50mg/50g
Soybean	<i>Glycine max</i>	<50mg/50g
Jackfruit	<i>Artocarpus integrifolia</i>	<50mg/50g
Elderberry	<i>Sambucus nigra</i>	<50mg/50g
Garlic	<i>Allium sativum L.</i>	<50mg/50g
Pea	<i>Phaseolus sp.</i>	<50mg/50g
Lentil	<i>Lens esculenta</i>	<50mg/50g
Broad bean	<i>Vicia faber</i>	<50mg/50g
Amaranth	<i>Amaranthus caudatus</i>	<50mg/50g
Barley	<i>Hordeum vulgare</i>	<25mg/50g
Rice	<i>Oryza sativa L.</i>	<25mg/50g
Rye	<i>Secale cereal</i>	<25mg/50g

Wheat	<i>Triticum aestivum L.</i>	<25mg/50g
Potato	<i>Solanum tuberosum</i>	<0.25mg/50g
Leek	<i>Allium porrum</i>	<0.05mg/50g
Onion	<i>Allium cepa</i>	<0.05mg/50g
Shallot	<i>Allium ascalonicum</i>	<0.05mg/50g
Cucumber	<i>Cucumis sativus</i>	<0.05mg/50g
Melon	<i>Curumis melo</i>	<0.05mg/50g
Pumpkin	<i>Curcubita máxima</i>	<0.05mg/50g
Tomato	<i>Lycopersicon esculentum</i>	<0.05mg/50g

*Data from e.g., Su and Tung [25] and Peumans and Van Damme [110].

If and how different lectins work together in concert is at present not known. Some combinations may be beneficial while others may not necessarily be so. In a pilot experiment (Aarra and Pryme, unpublished) showed that when lectin-rich berries and vegetables were combined in various amounts, the cytokine response in human lymphocytes changed with respect to what was seen when the plant extracts operated alone. Some responses were amplified while others were reduced. This is also the likely situation in the human body where the gut is constantly exposed to all kinds of lectins which constantly bind to receptors and mediate different responses, fine-tuned and balanced by the lectin components in the food we eat. There is still a lot of research that needs to be done to understand this area of human nutrition.

Toxic effects of lectins are based on observations related to isolated episodes. It is well known that ricin (from castor beans), a type 2-RIP, can cause death within the space of a couple of days if it injected so that it reaches the blood stream directly. Abrin and volkesein lectins are also known to be lethal toxins [2]. These, however, are present in plants that do not belong to our natural diet.

To be able to promote biological effects, lectins that are present in common foodstuffs have to be in a biologically active form and they must have the property of being able to bind to glycan receptors under the conditions that prevail in the GIT. Even though most lectins satisfy both criteria, the effects can be variable, depending on the type of lectin, its binding specificity and strength of binding [110,111]. The prevailing physiological conditions in the GIT (e.g. pH, level of bile salts, bacterial and yeast flora) will undoubtedly have an effect on binding effectivity and we can therefore expect great individual differences. Iliev et al [112] have in fact reported that the presence of a fungal community in the GIT (the so-called "mycobiome") that coexists with bacteria and greatly increases the repertoire of organisms that have the capacity to interact with the immune system of the intestine, thereby potentially having a major influence on health and disease. These workers have identified a polymorphism in the gene coding for Dectin-1 (a C-type lectin receptor) that is strongly associated with a severe form of ulcerative colitis.

Lectins that do not bind to the mucosa of the GIT, or are prevented from doing so, will be unable to induce biological effects through the mechanism indicated [12]. As mentioned earlier it is feasible, however, that some lectins may be taken up by endocytosis, are thus internalised and thereby will be in a position to promote a biological response. Such a response, however, will depend on how quickly the body is able to produce an antibody [113].

An experiment with rats given parenteral nutrition, to establish whether or not PHA and peanut Arachis hypogea lectin (PNA) could reverse GIT and pancreas atrophy was performed by Jordinson *et al* [114]. During a period of 4 days the rats received a continuous infusion of parenteral nutrition, and the test group a daily dose of lectins in addition. The results showed that both these lectins could prevent gastrointestinal atrophy that arose as a result of parenteral nutrition. Interestingly, their effects in the GIT were specific in that PHA had greatest effect on the fundus mucosa in the ventricle and upper region of the small intestine, while PNA was most effective in the large bowel. The observed effects of these lectins were partly attributed to direct binding of the lectin to the surface membrane and partly to a local lectin-mediated liberation of growth stimulating hormones, which in turn results in an increased synthesis and uptake of polyamines. This is an interesting example where two lectins from different sources were able to act positively in concert.

That plant lectins can modify the natural composition of the microflora in the intestine has been demonstrated by directly allowing these molecules to interact with lectins and agglutinating substances. It was seen that particular bacterial species in the intestinal lumen, could result in their selective elimination. Freed [115] has shown that lectins can prevent the binding of bacteria to the brush border membrane surface by increased cell proliferation, a modification of the level of glycosylation or by occupying binding sites for bacteria.

Banwell *et al* [116] performed an experiment where 2 groups of rats, one being bacteria-free, were fed a PHA-containing diet for 7 days and the intestinal flora was then checked. In contrast to rats maintained under bacteria-free conditions, "normal" rats

showed an overgrowth of *Escherichia coli* (*E. coli*). This experiment demonstrated that lectins can effectively modify the microflora of the intestine.

The oral feeding of PHA over time caused the normally thin and continuous mucous layer in the intestine to become thicker and uneven. Certain areas may thus lose their protection. This can theoretically lead to a weakening of the protective role that the mucous barrier plays in the intestine [115].

In parallel with the effects observed in the small intestine in rats, PHA in the diet also causes hypertrophy of the pancreas and promotes an increased secretion of digestive enzymes as a result of increased cholecystokinin (CCK) production [116-118]. This is a peptide hormone produced and released by I-cells, a type of glandular cell found in the wall of the duodenum. The hormone cholecystokinin (CCK) has several properties including a role in secretion of pancreatic enzymes, regulation of food intake, delay of emptying the ventricle and stimulation of contraction of the gall bladder.

Pusztai *et al* [118] have expressed the opinion that low doses of PHA can probably be useful as a therapeutic agent for patients with chronic pancreatitis since PHA is able to stimulate growth of the pancreas. Vasconcelos and Oliveira [119] have shown that PHA, in a dose-dependent manner, can have an effect on the endocrine pancreas by interfering with the secretion of insulin. In rats fed PHA the plasma insulin level was seen to fall while the blood glucose concentration remained unchanged. A variety of homeostatic processes are activated in order to compensate for the low insulin level. These include changes in levels of glucagon and glucocorticoids. Reduced insulin secretion results in increased secretion of glucagon that mobilises the breakdown of fat from depots.

That PHA may be useful as a dietary supplement or a therapeutic agent in order to stimulate GIT function, and in the treatment of obesity, has been suggested by Pusztai *et al*. [118]. First, however, it will be necessary to provide safe and effective doses in clinical trials.

It was shown by Kordas *et al* [120] that PHA has the property of binding to the gastric mucosa, and to parietal cells in the ventricle. The interaction resulted in a reduction in both endogenously and exogenously stimulated acid secretion. This has been associated with delayed emptying of the ventricle [119]. It has been suggested that certain plant lectins, for example those present in *Allium* species, may have promising probiotic effects.

The presence of lectins in elderberry fruit is well known [121] and the concentration is about 10mg/kg raw fruit. Of the three elderberry lectins in the fruit there is most of the SNA-IVf type while there are decreasing amounts of SNA-1f and SNA-Vf [see

Pryme and Dale [122] Table 8.4). Interestingly, Jiménez *et al* [123] have shown that elderberry lectins are refractory to proteolysis caused by gastric or duodenal fluids. Lectin-containing elderberry preparations have been successfully used by a number of authors for the relief of gastrointestinal ailments (e.g. [122,124-126]).

Systemic Effects

A systemic effect can be caused by biologically active lectins. This can be caused either by simulating the effects of endocrine hormones or they can bind to neuroendocrine cells in the GIT. This can lead to secretion of peptide hormones, which in turn can modulate the endocrine system [2].

Of the five main groups of heat shock proteins (HSP), the 70kDa family is the best studied. This protein is central in cancer since it suppresses apoptosis by inhibiting the caspase chain reaction [127] and thus has the function of a survival protein. It can also enter into a strong complex with mutated tumour suppressor protein p53 [128], and effectively obstructs it from entering the nucleus where it activates transcription.

A malignant tumour can be regarded as a tumour where, following a process of selection, cells have lost the ability to commit suicide (i.e., enter apoptosis) [129]. Over-expression of HSP70 has thus been observed in malignant tumours of diverse origin and increased levels are known to be associated with poor prognosis in cancer [130-132]. Rohde *et al* [132] have shown that if HSP70 is eliminated from a cell then apoptosis is spontaneously induced. Inhibition of HSP70 synthesis would therefore appear to be a novel and promising approach for treatment of human cancers, including those that show resistance to standard forms of therapy [133].

Pryme *et al* [100] have demonstrated that PHA, when added to the diet of mice, results in a great reduction in HSP70 levels in NHL cells growing intraperitoneally in mice. Briefly, two groups of mice were injected intraperitoneally with NHL cells; one group was maintained on a lectin-free diet while the second group was fed a diet containing PHA (7mg/g diet). On days 2, 3, 4 and 7 after injection mice were sacrificed and the peritoneal cavity was washed extensively with PBS to recover the tumour cells. Extracts were prepared from the harvested cells. Following electrophoresis and Western blotting to visualize HSP70, band intensity was determined and plotted as a function of duration of feeding PHA. The results showed that when a PHA-containing diet was fed to mice injected with NHL cells then a drastic reduction occurred in HSP70 levels in a time-dependent manner. After two days of feeding PHA the HSP70 level was already reduced by about 65%. Two days later the level had decreased to 10% of that expressed in NHL cells growing in mice fed a lectin-free diet. Seven days after injection HSP70 was virtually non-detectable.

What is striking with these observations is that the effect is seen after dietary intake of a normal plant protein. It would seem unlikely that PHA merely diffuses from the gut lumen into the intraperitoneal cavity since the molecule is a large 118 kDa protein [134]. As described earlier (and shown in Figure 1.1, Aricigil and Pryme, [12]) it is postulated that following lectin binding a second-messenger response evokes a stimulation of transcription and causes a subsequent release of biologically active molecules from the cells that are then able to induce a systemic response. It would appear that following entry into the bloodstream a factor is able to pass through capillary walls and into the intraperitoneal fluid thereby coming into contact with the NHL cells. Following uptake by the NHL cells transcription of the HSP70 gene would be rapidly affected, resulting in a rapid reduction in intracellular levels of the HSP70 protein. The result being reduced growth of the NHL cells. The consequences may be of extreme interest since it is evident here that a single dietary lectin is capable of inducing a response in the body that is detrimental to the growth of cancer cells.

Using a lectin-containing extract derived from Korean mistletoe Yoon *et al* [135] observed an anti-metastatic effect in a series of tumours where anti-angiogenic mechanisms were involved. In later experiments an induction of apoptosis was reported in tumours [136]. Similarly, using a purified lectin from Korean mistletoe, it was shown that mechanisms involving anti-angiogenesis and apoptosis were involved in reducing growth of a B16-BL6 melanoma in mice. Yoon *et al* [137] have described that the anti-tumour effect of the Korean mistletoe lectin can be attributed to the activation of both macrophages and NK cells. There are, therefore, a series of recent observations clearly indicating that the administration of plant-derived lectins can be beneficial in reducing tumour growth [138-141].

Even though mistletoe is not recognised today as a normal constituent of our diet, the plant was used widely in ancient times in folk medicine. This probably led to the development of receptors in the GIT having the property of binding mistletoe lectins. This could perhaps explain why ML-2 has been shown to bind to the FAE and VE areas in human Peyer patches (Table 1.4 in Aricigil and Pryme, [12]; [78]).

Industrially processed food forms an increasing part of everyday life. The means by which such food is prepared will often result in a loss (degradation, denaturation etc.) of biologically active molecules e.g., lectins. As mentioned above lectins can have extremely important functions and their "removal" from the diet would therefore not be desirable. A person closely following the blood type diet would probably eat lower amounts of processed food than non-followers, meaning that their diet would have a higher active lectin content. This may then afford an explanation for some of the positive effects that D'Adamo has described [142]. The

positive results that people have reported may well be explained by a general improvement in life style and health attitudes such as less fat, salt, sugar, more fruit and vegetables, reduced smoking, a lower alcohol consumption, and a higher level of physical activity. It is thus quite possible that the overall effect of D'Adamo's dietary recommendations have in fact been positive by increasing public awareness of what they eat. On the other hand his warning of the potential hazards of dietary lectins would seem to be unfounded. Accumulating scientific evidence in fact clearly indicates that dietary lectins are important constituents of our diet, along with vitamins, minerals, trace elements, antioxidants and the 3 and 6-omega fatty acids.

The observations described above strongly suggest that our diet needs to contain sufficient amounts of lectins in an active form in order for them to trigger the immune system. It is unfortunate that in general modern diets provide limited amounts of active plant lectins. Although there are exceptions such as the Mediterranean-type diet. A low level of lectin intake may perhaps mean that we are unable to maintain a high-level of immuno-surveillance. This will result in that we will be more prone to infections and other disorders, for example cancer. There is thus a strong case for dietary lectin supplementation, or at least a strong recommendation to increase the content of non-cooked fresh vegetables, fruit and nuts in our diets. In addition to improved NK cell levels, increases in serum levels of endostatin, TNF α and β -endorphin were recorded within a few days of ingesting the lectin preparation, indicating a relatively rapid biological response to the lectins [113]. These observations from normal, healthy individuals were in line with beneficial effects reported in cases of terminal cancer [100].

In their review González De Mejía and Prisecaru [15] discuss the inhibitory effects of plant lectins on malignant cells *in vitro* and summarise these as follows : (1) ingestion of lectins sequesters the available body pool of polyamines, thereby thwarting cancer cell growth, (2) they affect the immune system by altering the production of various interleukins, or by activating certain protein kinases, (3) lectins can bind to ribosomes and inhibit protein synthesis, (4) they can modify the cell cycle by inducing non-apoptotic G1-phase accumulation mechanisms, G2/M phase cell cycle arrest and apoptosis, and can activate the caspase cascade, (5) lectins can also down- regulate telomerase activity and inhibit angiogenesis.

Taken together, our knowledge obtained following the oral use of plant lectins and results from numerous positive *in vivo* and *in vitro* studies provide exciting opportunities for the development of new forms of handling cancer where these molecules are incorporated into novel treatment strategies. A specific example is afforded by the soybean lectin that has been shown to have anticarcinogenic potential. González De Mejia and Prisecaru [15]

discuss in their review potential use of lectins in cancer treatment, and correctly point out that much more research is required where both genomic and proteomic approaches should be included.

The future for lectins would seem to be promising. This further emphasises that a healthy diet should include large amounts of raw vegetables, fruit and nuts. In this way we can ensure a rich availability of these biologically active molecules that by all accounts exhibit beneficial effects on our well-being. What we need to know, however, is the stability of lectins under gastric and duodenal environments. For example, the elderberry lectins were shown by Jiménez *et al* [123] to be refractory to these conditions.

Most of our knowledge related to the nutritional effects of plant lectins is based on experiments using animal model systems, and only few studies have been performed on humans. The most frequently used lectin hitherto in animal studies is PHA, while equivalent studies using other types of lectins are unfortunately lacking in the literature. Since lectins are relatively specific proteins and various lectins can bind to different types of carbohydrate chains, it would therefore be incorrect to assume that PHA and ML-1-induced effects [95-100] will necessarily be characteristic for other lectins that we consume. A major reason for the frequent use of PHA is its availability since it amounts to 1-10g/kg raw kidney beans [111], thus representing a major protein in the bean. This is in contrast to lectins for example in onion, tomato, rice and banana where the concentration is <0.01g/kg raw material [111].

Winge *et al* [113] performed a small pilot study to evaluate whether or not a mistletoe lectin-containing preparation taken orally by adults was able to modulate the immune system. Eight healthy individuals (mean age 47 years) took the preparation daily for a period of three months and blood samples were taken both before and during the study. All individuals demonstrated the presence of anti-lectin antibodies in the blood on day 84, showing the occurrence of an immune response. No antibodies were identified at the start of the study. At the onset of the investigation it was surprising that 50% of the healthy individuals showed NK cell levels of between 6,7 and 12,5% i.e. well-below normal values (18-40%). Three of these showed increased levels after ingesting mistletoe lectins for 28 days, although the levels were not within normal limits. During the period of observation four cell types showed a marked response: activated IL-2 helper cells, memory cells, activated T-cells and activated natural killer (NK) cells. In general the levels of activated IL-2 helper cells and memory cells were elevated on day 28 with a return to normal levels on day 84. The levels of activated T-cells and the activated NK cells, however, were still elevated on day 84. At the start of the investigation four of the individuals had levels of NK cells that were well below normal values. At 84 days, however, three of these had values that were now within the normal range. It is likely that keeping the NK cell level

within normal levels is of major importance in order to maintain a potent first line of attack against virus and bacterial infections.

It was thus evident that in order to "prime" the immune system almost a third of the individuals had to take the lectin preparation for a period of three months in order to bring their NK cell levels within the normal range [113]. Keeping the NK cell level at normal values is not only imperative for maintaining an effective first line attack against for example, virus infections, but importantly it was shown many years ago that in animals exhibiting low NK cell levels then there is an increased risk for the development of both spontaneous and experimental tumours [143,144]. In addition, Yoon *et al* [137] showed that the prophylactic effect of a Korean mistletoe lectin-containing extract on tumour metastasis was mediated through the enhancement of the activity of NK cells. Takeda and Okumura [102] have reviewed a series of studies that have clearly identified a major role for NK cells in immune-surveillance.

The results presented here demonstrate that mistletoe lectins taken orally are effective as immunomodulators and thus a mistletoe preparation does not have to be injected (e.g. subcutaneously) in order to modulate the immune system in humans. The lectin-enriched mistletoe preparation described here appeared to effectively function as an immuno-stimulating dietary supplement for the healthy individuals who took part in the study. Of special interest was the increase in activated NK cells that was observed in several of the individuals who participated in the study. This is in line with Takeda and Okumura [102] who state that toll-like receptors and receptors to lectins, including those from mistletoe, are among the most likely candidates responsible for NK cell activation. It is interesting to note that lectins, also those from mistletoe, have recently been regarded as having great potential as anticancer agents [14]. In conclusion the mistletoe preparation described here, can be envisaged as a useful dietary supplement in order to stimulate the immune system in subjects where this would be beneficial e.g. in immunodeficiency. Such a preparation could also be beneficial for the public at large in order to "prime" the immune system such that, for example, the unpleasant effects of common colds and flu may be greatly reduced. In addition, the body will in general be more suited to combat other types of bacterial or viral infection, and, furthermore, be able to operate more effectively in the inactivation/destruction of abnormal cells in the body (e.g. cells of precancerous nature, or even tumour cells themselves).

As mentioned above there are a series of observations that clearly indicate that mistletoe lectins can induce the induction of an anti-angiogenic response. It was therefore interesting to note that serum endostatin values showed increases within a few days of the oral intake of the lectin preparation. These results would suggest that oral intake of mistletoe lectin was able to induce an anti-angiogenic response. The observed increase in TNF α values in

the blood within a short time after oral intake of mistletoe lectins is in agreement with other findings showing induction of TNF α production following subcutaneous administration of ML [145-147]. Elevated levels of β -endorphin in the blood as a result of the oral consumption of a mistletoe lectin preparation are in line with the results of Heiny and Beuth [148] and Heiny *et al* [149] who showed increased plasma levels of β -endorphin after treatment of breast cancer patients with standardized mistletoe lectin extracts. It is not known from this pilot study whether the observation that TNF α values increased in parallel with increased levels of β -endorphin values is a matter of coincidence or is indeed of some biological significance. Clearly, further work will be required to provide concrete evidence that the observed changes in endostatin, TNF α and β -endorphin values in response to oral intake of the mistletoe preparation are important.

Antibodies to mistletoe lectins have been detected in humans after subcutaneous administration [150-152]. We show here that the consumption of a mistletoe lectin preparation by adult's results in the induction of antibody production against mistletoe lectins. After drinking the preparation for 84 days all 8 individuals were observed to have produced ML antibodies. This is in line with previous observations where oral presentation of ML to mice resulted in the appearance of specific serum IgG and IgA antibody after three oral doses [108]. As expected different epitopes were detected since ML-I antibodies cross-react, for example with ML-III.

There are many dietary supplement preparations commercially available where claims are made that they are immunostimulatory when taken orally. Documentation of these claims, however, is in on the whole sadly lacking. In this study two lines of convincing evidence were presented that the mistletoe preparation described has potent immuno-stimulatory properties, firstly, four cell types of the immune system showed marked proliferation, and secondly, all individuals produced antibodies to the lectins present.

By using the oral, as opposed to the subcutaneous route, the possibility of an allergic reaction is reduced and a much more far-reaching, long-term effect is observed [153]. About 80% of immunoreactive tissue in the body is associated with the gastrointestinal tract. Following consumption of mistletoe lectins, they work by binding to specific galactose/N-acetylglucosamine receptors on M-cells of Peyer's patches associated with the MALT/GALT system [78]. Subepithelial lymphoid follicles provide the most important sites for antigen sampling in the small intestine and constitute an effector mechanism for secretory immune responses of GALT [154]. The importance of this mechanism is two-fold, firstly an immune response is vital such that protection of host tissues against invading microorganisms can operate, and secondly that the extent of an infection can be curtailed as much as possible [155]. Lymphoid follicles are overlaid by the follicle-associated

epithelium (FAE) that includes a number of cell types such as lymphocytes, enterocytes, goblet cells, M-cells and pre-M-cells [156]. In studies on specimens of human small intestine containing Peyer's patches Sharma *et al* [78] showed by histochemistry that mistletoe lectin bound to both enterocytes and M-cells of the FAE. It is therefore evident that the surface of the small intestine in humans contains receptors that bind mistletoe lectins (see Table 3 in Sharma *et al* [78]).

Following binding to receptors lectins causing a release of signal molecules to the blood and these are then able to stimulate the immune system and also induce an anti-angiogenic response [113]. Helper cells show a fast initial response, whereas cells involved in immuno-memory show a slower but prolonged increase. This, however, was as expected since populations of memory cells are quite stable and do not need to be activated to have an impact on the immune system as do the helper cells.

Interestingly, it was observed that the individuals who in general showed the weakest reaction were those who had initial values above normal limits, whilst those who demonstrated the highest response had values below normal at the onset of the study. The results suggest that the higher the starting (normal) values, the lower the response and vice versa, which is in agreement with other observations [102].

Although present in many foodstuffs of plant origin [14] lectins are denatured by heat treatment and thus cooking, frying etc. will reduce their immune-stimulating potential virtually to zero. Since there are many lectins which have specific receptors in the human small intestine [78] it is evident that our diet needs to contain a certain quantity of these molecules in an active form in order for them to trigger the immune system. Modern diets unfortunately provide limited amounts of active plant lectins, perhaps insufficient to achieve high-level immunosurveillance. This will mean that we will be more prone to infections and other disorders.

It has been shown that obese and diabetic patients have a greater susceptibility to develop cancer than lean and non-diabetic individuals. Furthermore, it is well known that a diet rich in saturated fats and red meats and at the same time low in fresh fruits, vegetables, and whole grains favours an increased risk of cancer. According to the United States National Institutes of Health "12 servings of fruits and vegetables a day" can prevent the development of common diseases, including cancer [38].

In their paper Su and Tang [25] measured the lectin content in 20 non-cooked fruit and vegetable extracts (50 g amounts). Based on relative lectin levels (as measured by haemagglutination activity), what was surprising was the large differences observed: chili, Chinese cabbage, garlic, ginger, lemon and passion fruit had a content of 64, while banana, grapefruit and Kiwi had 32. Apple,

grape and pineapple had 16, lettuce and orange 8, melon, onion, plum and strawberry 4, while watermelon had 2 and carrot 1. For example, it was interesting that lemon (64), grapefruit (32) and orange (8) i.e. all belonging to the citrus fruits, should vary by a factor of 8.

Lectins are also ubiquitous in our food supply, mainly in legumes, like beans and soybean which can vary greatly in lectin content. Other legumes may contain 20g of lectin per 100g of flour. These include cereal type foods (187.2µg of lectin/g) and texturized protein flour (53µg lectin/g) [32]. In addition to legumes, other foods may contain considerable amounts of lectins, like the cereal amaranth (8.3%), corn (0.8%) [157]. On the other hand, meat substitutes are free in active lectin content, and extremely low levels are found in bakery products [157].

The Mediterranean Diet

If we consider a newly prepared salad that contains perhaps 10 fresh ingredients (Table 2), then the spectrum of lectins that we would be exposed to during the course of a meal, would be wide (up to 50). Perhaps the success of the Mediterranean-type diet (MedDiet), rich in plant-based material, that is now highly acclaimed for its positive effect on health, is at least in part due to a rich and varied lectin content. For the third year in a row the MedDiet has been claimed by the U.S. News and World Report as the world's best healthy diet [3]. In this class of diet, which has a high content of fruits, nuts, vegetables and whole grains, one can find >200 individual components that are rich in these foodstuffs (Table 1). The MedDiet has been looked at in many studies for its favourable effects on health, and professionals at the Mayo Clinic, where claims that the risk of developing cancer, Parkinson's and Alzheimers disease, and cardiovascular disease, have been put forward [158].

The MedDiet sails up as the brain's favourite food. A number of observational and intervention studies have shown that the MedDiet best protects the brain and prevents cognitive failure [159-161]. This diet consists of many unsaturated fats from olive oil, nuts and seeds, more fish and seafood, more legumes, fruit and vegetables and less grain. Around the Mediterranean they drink red wine and water for meals, not milk. They eat some dairy products in everyday life, such as sour yogurt, fresh kefir and flavoured and often unpasteurized cheeses. These are, however, extremely low in lectins. They do not eat large amounts of meat on the grill, but just stick to portions of well-ripened Parma and Serrano ham, and eat vegetables and fruit. On cool evenings, they can heat up soups of squash, broccoli, and peas, mixed with plenty of fish, and Parmesan and olives. Fresh vegetables and fruits are frozen in season and ensure good health during a cold winter.

A large study published in the British Medical Journal showed that a MedDiet with extra fat and nuts posed a much lower risk of

dementia than lean diets. A total of 969 elderly (44.6% men aged 74.6 +/- 5.7 years) participated in the study. They were cognitively tested and randomized to a MedDiet with 1 liter of extra virgin olive oil per week or a MedDiet with 30g unsalted nuts a day (15g walnuts, 7.5g hazelnuts and 7.5g almonds). The control group received low-fat diets. After 6.5 years of mapping, 522 elderly persons underwent thorough neuropsychological mapping. Both MedDiet groups had far better cognitive function than those fed the lean diet [162]. The diets of olive oil and nuts worked independently of age, educational level, strain of cognitive failure in the family, dementia, cardiovascular disease, physical activity and caloric intake. The researchers explain the effect as being due to reduced inflammation and less oxidative stress. They also explain some of the effects of the MedDiet in the so-called PREDIMED study with a sharp reduction in oxidative stress using antioxidants from both red wine, espresso, extra virgin olive oil, olives, nuts and polyphenol-rich vegetables. The rest they add to a muffled inflammation throughout the body. At the same time, it is generally agreed that a Western diet rich in refined carbohydrates weakens the brain, especially the memory pathways. At the same time, scientists agree that a Western diet rich in refined carbohydrates weakens the brain, especially the memory pathways. This diet produces a malfunctioning hippocampus, and the result is impaired learning and memory.

Most experiments with lectins conducted in animals have used high doses and these have in general been conducted over relatively short periods of time. We know virtually nothing about long-term effects of exposure. It would be extremely problematical and practically difficult to test the health-related effects of plant lectins in humans. It is not such that we ingest a single type of lectin. Plant lectins are widespread in diets consisting of raw vegetables, grains, fruit and nuts and have therefore been consumed by mankind for thousands of years. From Table 1 it is evident that our food contains more than 200 lectins. The fact that fruits, vegetables and nuts can contain up to 5 different lectins means that the true number we ingest is perhaps close to 1000.

As mentioned earlier the MedDiet provides a rich source of lectins, and persons that live for example in Greece, Italy, France and Spain are thus continually exposed to a wide variety of lectins. Their general health would appear not to be inferior to that in northern Europe, in contrast perhaps superior. One is thus tempted to conclude that a diet rich in lectins is highly advisable. For example, van Buul and Brouns [162] showed that consumption of cereals and whole grain products was associated with significantly reduced risks of cardiovascular disease, type-2 diabetes and some cancer types, where wheat germ agglutinin (WGA) is an important constituent.

In general, potential hazards of dietary lectins would appear to be unfounded. Scientific evidence currently accumulating clearly

indicates that lectins are in fact important constituents of our diet, and will in due course be acknowledged as such along with the already well-accepted vitamins, minerals, trace elements, 3 and 6-omega fatty acids, antioxidants and fibre etc [163].

Interestingly, data presented by Rissanen *et al* [164] have shown that a high intake of fruit, berries and vegetables is associated with reduced risk of mortality in middle-aged Finnish men. These findings would indicate that diets rich in plant-derived foods (i.e. lectin-enriched) can promote longevity. Beattie [165] have similarly concluded that there is considerable evidence that an adequate consumption of fruit and vegetables is advisable. This is to prevent the occurrence of a series of chronic diseases such as stroke, several cancers, and heart disease. More specifically Brennan *et al* [166] have provided data that strongly suggest a substantial protective effect on the consumption of cruciferous vegetables on lung cancer. Thole *et al* [167] have shown that elderberry fruits have a major chemopreventive effect on cancer development, while Pryme and Dale [122] in their review reported on the positive effect of elderberry lectins on gastrointestinal disorders.

Conclusions

There are still many unanswered questions concerning possible effects of plant lectins in our diet on general health. Results published in the literature cannot in any way be interpreted such that there are indications enabling us to suspect that dietary lectins give rise to disease. On the contrary the fact that health authorities worldwide promote the "5 a day" (or even "7 a day") principle, namely that we should include a minimum of 5 portions of vegetables, fruit and nuts (i.e. lectin-containing foodstuffs) in our daily diet would clearly indicate that there are health-benefits associated with increased lectin intake. However, taken together there is little doubt that more intensive research efforts are required in order to be able to draw firm conclusions regarding potential health-promoting effects of dietary lectins. A major task will be to establish satisfactory scientific guidelines to pursue such studies and interpret results. It is evident that we are only at the very beginning with respect to gaining an understanding of the importance of lectins in our food with relation to health and nutrition [168-170].

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