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BLUEBERRY AND HUMAN HEALTH: A GUIDE TO OPTIMAL WELLNESS

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ABSTRACT

Blueberry is a kind of perennial blooming plant that yields berries that are either blue or purple. They belong to the genus Vaccinium, which is found around the world. It is a subfamily of the Vacciniaceae family and a part of the Ericaceae family. Native Americans were the first to use them extensively. Anthocyanin, which is abundant in blueberries, possesses numerous anti-oxidant, anti-tumour, anti-diabetic, antibacterial, cardioprotective, and anti-hypertensive qualities. Because of its remarkable properties, several research has been carried out to evaluate the health advantages of this chemical. A wide range of cosmetic products, such as facemasks and face washes, employ blueberry extract because of its high vitamin C and K content. These are commonly used as food supplements since they are an excellent source of antioxidants and have anti-obesity properties. This article covers a wide range of topics related to blueberries, including their history, cultivation, phytochemical components, health advantages, side effects, natural therapies, market formulation, and some current research.

1. INTRODUCTION

Blueberry is a kind of perennial blooming plant that yields berries that are either blue or purple. They are worldwide members of the Vaccinium genus, which is a subfamily of the Vacciniaceae family and a member of the Ericaceae family. They are classified as members of the Cyanococcus section. These are little, rounded, edible plants. The blueberry blossom is either pale pink or whitish, while the leaves are elliptical.[87,88] There are about 450 species in this genus, which include the huckleberry (*Vaccinium parvifoium),* bilberry (*Vaccinium myrtillus L.*), lingonberry (*Vaccinium vitis-idaea L.*), and cranberry (*Vaccinium macrocarpon Ait.).*[2] The name or abbreviation that comes after the species designates the individual who

gave it its original name; for example, the letter "L" stands for Linnaeus.[89] Other berries in this genus include Madeira blueberries, huckleberries, bilberries, and cranberries. Both the cultivated (highbush) and wild (lowbush) blueberries that people purchase in the grocery store are native to North America.[1]

Blueberries are available in three main varieties: the wild lowbush (*Vaccinium. angustifolium*), the cultivated highbush (*Vaccinium corymbosum*), and the rabbiteye (*Vaccinium virgatum, syn. Vaccinium ashei*).[3] When it comes to soil and weather, different blueberry varieties have different needs. For example, lowbush blueberries are often found in abandoned pastures and can withstand a wide range of temperatures. Conversely, only cooler climates are favourable for the growth of northern highbush blueberries, whilst warmer climates are more suited for southern highbush blueberries, which are a hybrid of various species such as *V. corymbosum, Vaccinium angustifolium, Vaccinium darrowii, Vaccinium ashei, and Vacc tenellum.*[4] Wild blueberries *V. myrtillus* is a type of blueberry grown dominantly in Italy this blueberry is a major source of antioxidants.[85] Wild blueberries also help in neuronal inflammation.[86]

The first people to appreciate blueberries' many uses and health advantages were the Native Americans, who used them as a natural flavouring and medicine.[5] Though they were first successfully grown in 1912, Native Americans have relied on blueberries as a food source for millennia. Because of their extended shelf life, they were a significant feed crop that was dried and stored for the winter. During their season, they were eaten fresh and added to a variety of cuisines. Additionally, the Native Americans employed various Vaccinium species parts for therapeutic purposes. When highbush blueberries were introduced to Europe in the 1930s, their understanding of the berries and their growth patterns greatly affected the creation of contemporary blueberry types.[6,1] Due to its numerous health advantages, blueberries were termed a "superfood" by researchers in the 1990s and early 2000s. The result was a surge in blueberry output in the United States, which increased from approximately 100 million pounds per year in the late 1990s to over 500 million pounds in the most recent years.[6] They have been extensively utilized for millennia in China as a traditional medicinal plant for the prevention of glaucoma premature greying, and anemia.- The main goal of breeding initiatives in the early 1900s was to increase the distribution of highbush blueberry types throughout North America's temperate zones. By the 1940s, the goal had changed to include expanding their geographic range to include the warmer southern

states of the United States. The development of southern highbush varieties, which have excellent fruit attributes, such as larger fruit sizes with better flavour and texture was made possible by breeding northern highbush blueberries with wild southern species. The plant also demonstrated characteristics such as fruit persistence in warm conditions, great bloom, rich flavour, and evergreen status.[3,4,7] The height of a highbush blueberry varies from 5 to 23 feet. Although additional species have been used in contemporary breeding operations, the two species V. corymbosum L and V. austral Small are mostly responsible for the development of the cultivated highbush blueberry.[89] Because of their high anthocyanin content, blueberries have drawn attention from academics due to their potential health advantages beyond just being antioxidants. Both in vitro and in vivo methods have been used to assess these possible health benefits.[83] Anthocyanins are the important bioactive component in blueberry This anthocyanin plays a key role in the therapeutical benefits of blueberry The anthocyanins (Greek antos, flower and kyanos, blue)[82] or Phenyl-benzo-γ-pyran, are made up of two phenyl rings and a heterocyclic ring these are the chemicals soluble within water.[77,78] They are sometimes referred to as 2-phenyl benzopyrylium cations.[78] Certain fruits and veggies colours such as blue, violet, purple, red, pink, and orange are brought by anthocyanins.[79] According to some studies, blueberries have more anthocyanin contents than raspberry and strawberry[80] non-glycosylated anthocyanin are referred to as anthocyanidin they possess OH group[77] most available anthocyanidins are pelargonidin, cyanidin, and delphinidin, peonidin, petunidin and malvidin;.[77] These anthocyanins donate their proton to the dangerous reactive free radical and make them unreactive. Capillary electrophoresis is a method used for the separation of anthocyanins.[81] In retinal and endothelial tissue cells, blueberry anthocyanins mitigated the oxidative stress resulting from elevated glucose levels. Research has demonstrated that anthocyanins alter gene expression to lower the production of inflammatory cytokines, which may have anti-inflammatory benefits. Blueberries have recently been shown to assist people when they are engaged in cognitive tasks.[83] The numerous health advantages of blueberries can be attributed to their high phenol content. However, the plant contains many bioactive substances in all of its other sections in addition to the fruit. Blueberry leaves are utilized as a dietary supplement and have been shown to have a variety of therapeutic benefits, including preventing mice from gaining body fat and having neuroprotective properties.[8,9,10] Remarkable is the finding of a recent study that a certain blueberry cultivar called V. virgatum Aiton has proanthocyanidin derived from leaves that has strong inhibitory effects on the replicon cell system's ability to create the Hepatitis C virus subgenome.[10] Highbush blueberry leaf extracts have demonstrated strong antibacterial

activity in the literature to date, primarily against Salmonella Typhimurium and Enterococcus faecalis.[11] Additionally, *Staphylococcus aureus*, *Salmonella enterica*, *Enterococcus faecium*, *Listeria innocua*, and *Bacillus* cereus are all susceptible to the antibacterial properties of blueberry leaf extract.[12] Studies have revealed that the blueberry plant's leaves and fruits are abundant in bioactive substances with antioxidant qualities. This review's goal is to provide an updated summary of the most recent research on the employ YED approach.

2. GEOGRAPHICAL DISTRIBUTION, COLLECTION AND CULTIVATION

The United States is the world's greatest producer of blueberries. In addition, Colombia, British Columbia, Chile, and Argentina grow them. 38 states allow the commercial cultivation of blueberries, with Michigan producing the most, along with New York, New Jersey, and a few other nations.[13] The projected acreage of North America increased by 13.8 per cent over two years, from 95,607 to 108,791 acres, between 2008 and 2010 (NA1&NA2). This represents a total of 13,184 extra acres.[14] As of 2010, North America accounted for about 57% of the global blueberry acreage, with over 100,000 planted acres. With 3,950 new residents in the south and 7,765 new residents in the west, the two regions continue to develop at the quickest rates. Mexico has shown rapid growth, rising from a low acreage of 857 in 2008 to 56 million pounds in 2010. Significant production gains were also observed in North Carolina, Oregon, Washington, and British Colombia (NA 4). The increase in North American output from 415.8 million pounds to 419.3 million pounds, with the great majority, is also remarkable. North America is still a major force in the world market. The 2010 North American season will receive careful consideration due to its importance in the global marketplaces for processed and fresh food as well as the notable changes that have occurred in the past year. In[14] After being grown, blueberry plants yield between 400 to 800 pounds of blueberries in their third year of production. Five to seven years after planting, full crops are attained, yielding two to three tons of blueberries annually from a complete blueberry plant. Usually planted in the middle of April, blueberry bushes need about eight hours of sunshine and hydration. Blueberries should be planted in clay soil with a pH range of 4.0 to 5.2 to promote better growth. Row spacing for plants should be 4 feet apart and between rows, 9 feet apart. It is recommended to water the plants once a week but as blueberries have delicate roots in their first year, fertilizers should not be applied. Blueberries self-pollinate. In the fourth year, they undergo trimming, and the first two years' blossoms are eliminated to encourage greater growth. Furthermore, blueberry seedlings can be made by covering newsprint, spreading blueberry seeds on sphagnum moss, and keeping the mixture at 70 degrees

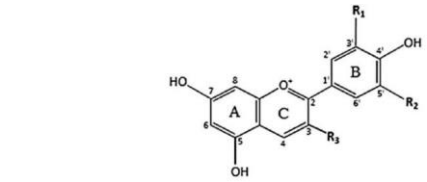
Fahrenheit until planting.[15,16]

3. PHYTOCONSTITUENTS

Blueberries are often called super fruits due to their rich nutritional content. They contain high amounts of dietary fibre, which accounts for 2.4% to 3.5% of their fruit weight. They also have smaller amounts of vitamins A, B, and E and are an excellent source of C and K[17,18,19]; moreover, vital elements including calcium, iron, magnesium, manganese, and zinc are found in blueberries.[20,21] Additionally, they contain bioactive compounds, including polyphenols like anthocyanins and flavanols[22], phenolic acids[23] and carotenoids like lutein.[19,22] Secondary metabolites in plants called phenolic and polyphenols serve as defence mechanisms against environmental stressors like excessive light, UV rays, adverse temperatures, water shortages, salt, nutritional deficiencies and pathogenic infections.[24] Plants contain natural pigments called anthocyanins, which give fruits, flowers, leaves, and some vegetables their vibrant red, blue, and purple colours. In addition to improving a plant's aesthetic appeal, these pigments are essential for pollination and seed distribution. The flavylium cation (C6-C3-C6) makes up the fundamental structure of anthocyanin that can be attached to different sugars, as well as hydroxyl and methoxy groups. Till date, more than 635 anthocyanins have been discovered.[25] An extensive range of models, including human epidemiology, clinical trials, screening, and mechanistic research in animal and cell culture models, have been used to extensively examine the possible health benefits of anthocyanins. In the multivariate model, there is an inverse relationship between dietary anthocyanin intake and cardiovascular events, such as myocardial infarction and mortality from coronary heart disease and cardiovascular disease. Randomized clinical trials (RCTs) have demonstrated that dietary sources of anthocyanins, such as cranberries, blueberries, and strawberries, enhance atherogenic lipid profiles, including total and LDL cholesterol reduction, HDL cholesterol elevation, and lipoprotein particle size patterns.[25] Anthocyanins also show promising anti-tumor activity in some cancers. Research demonstrates that maturity, environment, and heredity all affect the polyphenol concentration of blueberries.[26] Table 1 represents the composition of bioactive components in blueberry. Figure 1[76] depicts the structure of Anthocyanin and its types.

Table 1: Depicts the bioactive components of blueberry.

NUTRITIONAL COMPOSITION	Mg/100g	REFERENCE
Vitamin A	5.0-83.1	[18]
Vitamin C	3.4-9.5	[18]
Vitamin E	0.57	[27]
Vitamin K	56.1-79.9	[18]
Vitamin B1	19.6-26.7	[18]
Vitamin B2	38.0-70.2	[18]
Vitamin B3	1.0-1.7	[18]
Vitamin B6	0.052	[27]
SULPHUR	10.1-25.4	[2]
COPPER	0.01-0.09	[21]
MOLYBDENUM	0.003-0.012	[21]
BORON	0.08-0.14	[21]
PHOSPHORUS	6.8-20.3	[21]
IRON	0.15-0.57	[18]
ZINC	0.06-0.13	[18]
CALCIUM	6.6-15.2	[21]
NITROGEN	74.4-103.1	[21]
MAGNESIUM	4.5-10.1	[21]
CALCIUM	6.6-15.2	[21]
POTASSIUM	66.2-98.0	[21]
TOTAL PHENOLIC CONTENT	393±52	[27]
TOTAL FLAVONOIDS	2.5±387.48	[28]
ANTHOCYANINS	233±34	[27]
MALVIDINS	22-33%	[29]
DELPHINIDINS	27-33%	[29]
PETUNIDINS	19-26%	[31]
CYANIDINS	5.7-14%	[31]
PEONIDINS	1.4-4.5%	[31]
FLAVONOLS	38-46	[27,29]
QUERCETIN	24	[29]
MYRICETIN	26	[30]
FLAVANOLS	1.1	[30]
LUTEIN	1.53	[19]



		R1	R2	R3		R3
Most common anthocyanidins	Pelargonidin	-H	-H	-OH	Anthocyanins	-O-sugar
	Cyanidin	-OH	-H	-OH		-O-sugar
	Delphinidin	-OH	-OH	-OH		-O-sugar
	Peonidin	$-OCH_3$	-H	-OH		-O-sugar
	Petunidin	$-OCH_3$	-OH	-OH		-O-sugar
	Malvidin	$-OCH_3$	$-OCH_3$	-OH		-O-sugar

R_1, R_2, R_3–chemical groups

Fig. 1: The chemical composition of the primary anthocyanidins and anthocyanins found in blueberry.[76]

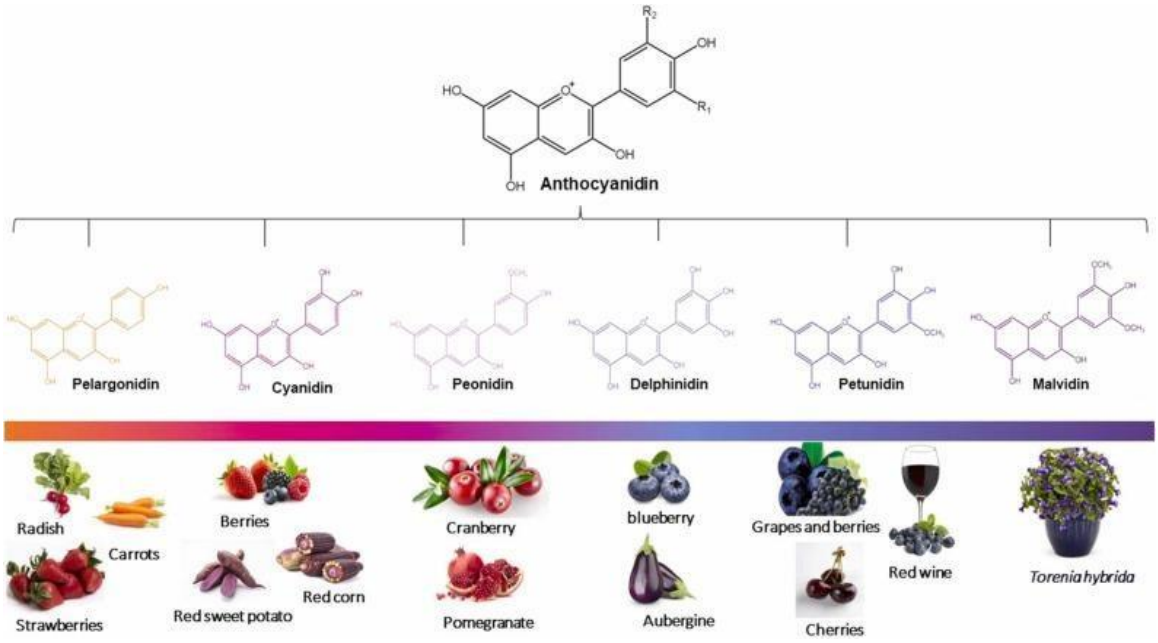


Fig. 2: Overview of the relationship between the colour and chemical structure of cyaniding.[76]

4. USES

One class of flavonoids with various health advantages is anthocyanins; blueberries are considered one of the greatest suppliers of these compounds. According to studies, eating blueberries daily may help prevent the onset of diabetes, obesity, and pulmonary arterial hypertension. Furthermore, it has been discovered that blueberries contain outstanding antioxidant, anti-inflammatory, anti-tumour, and cardio- protective qualities that can help lessen oxidative stress in the body. Blueberries have been the subject of numerous research to assess their efficacy because of their possible health advantages. A number of these researches have shown how beneficial blueberries are to one's health.

Blueberry extract's cardioprotective effects in isoproterenol-induced cardiac hypertrophy

Isoprenaline, a selective beta-adrenergic receptor agonist, was utilized in this experiment to induce heart hypertrophy in male albino rats, demonstrating the cardioprotective activity of the blueberry extract. Though the precise mechanism of isoprenaline's cardiotoxicity remains ambiguous, studies suggest that one possibility is that isoprenaline causes elevated oxidative stress (Kater et al. 2017).

Male albino rats were utilized in the 30-day trial, and they were split into six groups, A, B, C, D, E, and F. Group A, the control group, was given 5 mg/kg of distilled water daily by gavage for 28 days. Group B underwent daily subcutaneous injections of isoprenaline at a dose of 5

mg per kilogram of body weight from day 15 until day 28 of the experiment. Groups C, D, and E received blueberry extract from day 1 to day 28. The extract was administered to each group in turn at doses of 25 mg per kilogram of body weight, 50 mg per kilogram of body weight and 100 mg per kilogram of body weight After one hour of the blueberry extract administration, on day 15, isoprenaline (50 mg/kg/day) was subcutaneously injected into each of these groups. From day 1 to day 28, Group F received only 100 mg per kilogram of body weight of blueberry extract every day. Day 29: All of the groups' rats underwent electrocardiogram recording, blood was drawn from the retro-orbital plexus, and allowed to clot, and the animals were sacrificed so that measures of their body weight, heart rate, and tail length could be taken. The samples were promptly frozen in liquid nitrogen and kept at a temperature of -80°C until the analysis, which happened on the thirtieth day. The heart specimens were kept in 10% buffered formalin for 24 hours for histological investigations.

While group B's ECG revealed larger R and T waves, bradycardia, and a low heart rate, group C's ECG revealed normal values. The baroreceptor reflex brought on by the decreased heart rate may be one of the causes. In addition, there were dose-dependent alterations in the ECG, with group D (50 mg/kg/day) exhibiting the best ECG in comparison to the control group. Troponin levels were assessed using an ELISA kit, and the blood serum's Aspartate aminotransferase, creatine kinase isozyme-MB and lactate dehydrogenase were evaluated spectrophotometrically. As it turned out, group B had higher than the control group levels of these enzymes at 113%, 157%, 53%, and 169%. The enzyme level in the group that consumed blueberry extract alone stayed constant. When compared to group B (isoprenaline administered solely group), the 50 mg/kg group demonstrated a significant drop in the blood enzyme level. In contrast, the pre-treated group's enzyme levels were lowered by the blueberry extract supplied. Antioxidants were found to be low in Group B and oxidative stress markers such as glutathione, lipid peroxidase, and catalase activity were enhanced. They were discovered to be low in group F and control. Only the 50 mg/kg group out of the other groups exhibited significant antioxidant content and low levels of these markers, similar to the control group. This explains how blueberry extract's antioxidant properties contribute to its cardioprotective effects. Using the ELISA kit to assess the inflammatory markers, it was discovered that the isoprenaline-only group had Interleukine-6 and Tumor necrosis factor-alpha levels that were two to three times higher than those of the control group. Comparing the 50mg/kg group to the others, the levels were noticeably lower. Using immunohistochemical staining, the activity of nuclear factor NF-kappa-B p65 and

Cyclooxygenase-2—two crucial regulators for the expression of genes encoding cytokines and inflammatory molecules like Tumor necrosis factor-alpha was observed in the heart tissue. The group receiving isoprenaline alone demonstrated a 272% increase in p65 activity in contrast to the control group. According to the histological investigations, the cardiac tissue histology of groups A and F was normal. The cardiomyocyte cross-sectional area increased in the isoprenaline-intoxicated group, indicating cardiac hypertrophy. The cardiomyocyte bundles in the 25 and 50 mg/kg pre-treated group were normal and free of damage. The heart tissue of the 100 mg pre-treated group exhibited discernible degenerative alterations.

The study concludes that the reduction in oxidative stress in the heart tissue caused by isoprenaline accounts for the cardio-protective action of the blueberry extract. Furthermore, it is noted that compared to the other groups, the 50 mg/kg dose exhibits a superior cardio-protective effect.[32]

Blueberry Extract's Comprehensive Approach to Lung Function in Pulmonary Arterial Hypertension

In a study, Patrick Turck and team examined how blueberry extract affected the pulmonary redox state and right ventricle function in mice given monocrotaline injections to induce pulmonary arterial hypertension. Five groups of male stat rats were employed in the investigation. The monocrotaline group got an intraperitoneal dosage of monocrotaline at a dose of 60mg per kilogram of body weight while the control group (CTR) was given a simple saline solution. The blueberry extract was pre-treated for two weeks at doses of 50 mg, 100 mg, and 200 mg per kilogram of body weight and then the remaining three groups were given monocrotaline for three weeks. Five weeks were dedicated to the study. After the investigation, a hemodynamic assessment was conducted to determine the mean pulmonary artery pressure and the right ventricle was examined using right ventricular catheterization to evaluate heart function. Following the sacrifice of the rats in each group, lung tissues were gathered for analysis. The lung samples underwent homogenization, centrifugation and redox state analysis. Standard procedures were used to assess the samples' total reactive species, total nitrite content, NADPH oxidase activity, carbonyl content, lipid oxidation, catalase, glutathione peroxidase, and superoxide dismutase activities.

Since sulfhydryl content has an antioxidant impact that is not mediated by enzymes, it was also examined. The lung tissue was exposed to Western blotting to assess the oxidative stress and to measure the levels of xanthine oxidase, catalase, Cu/Zn-Superoxide dismutase (SOD1),

endothelin B receptor, and endothelin A receptor. Using right ventricular catheterization, it turned out that the Monocrotaline-treated group's right ventricle's E/A ratio was lower than that of the control group. There were variations between the Monocrotaline and control groups and the other Blueberry groups. Results for the Blueberry extract 100 mg/kg group were comparable to those of the control group, suggesting a modest improvement in the tricuspid valve and right ventricle flow. The study found that the Monocrotaline group's lungs had much higher levels of reactive oxygen species and xanthine oxidase expression, but the blueberry extract groups had significantly lower levels of ROS, suggesting that the extract had anti-oxidant properties. Superoxide dismutase activity was recovered in the MCT+100 mg/kg group; however, there was no increase in the Cu/Zn Superoxide dismutase enzyme. Additionally, compared to the control group, catalase activity was decreased in the MCT and MCT+100 mg/Kg groups. Both MCTs had lower levels of Nrf2 expression than the control group. The group that received Blueberry extract, particularly the 100mg group, demonstrated the restoration of this factor expression in the lungs. This suggests a decrease in reactive oxygen species (ROS) and an elevation in antioxidant signalling within the tissue, both of which are positive indications of redox balance. In the MCT group, the Endothelin A / Endothelin B receptor ratio [ETAR/ETBR] elevated particularly when the group's endothelin A receptor was more expressed. In lung tissue, these factors' expression was reinstated in the BB+100mg/Kg group, which did not exhibit any differences from the control group. Given that one of the causes of PAH is reduced vasoconstriction, a low Endothelin A / Endothelin B receptor ratio suggests reduced vasoconstriction, these suggest that BB extract induces less severe vasoconstriction and pulmonary vascular remodelling following pulmonary arterial hypertension. In the end, there was an increase in sulfhydryl concentration in the lungs, suggesting that antioxidant activity had returned.

Although there was no discernible variation in the levels of Nitrate (NO) among the pulmonary arterial hypertension-induced groups, it is hypothesized that the reduction in reactive oxygen species may have increased the bioavailability of NO in the lungs. This is because elevated reactive oxygen species decrease NO availability by reacting with NO to form peroxynitrite. Peroxynitrite can decompose into hydroxyl radicles and the body lacks an antioxidant system to contract them.

Overall, the results of this study indicate that blueberry extract does reduce Pulmonary arterial hypertension. It functions by lowering oxidative stress and enhancing the lungs'

antioxidant system, which may be contributing to pulmonary arterial hypertension.[33]

Triple-negative breast cancer and blueberry

When human epidermal cells, receptor progesterone receptors, and estrogenic receptors are absent from tumour cells, the malignancy is referred as triple-negative breast cancer. Normal cancerous cells, on the other hand, have all three of these receptors.[34]

The present investigation examines the effects of 5% and 10% blueberry powder on the capacity for metastatic spread of MDA-MB-231 tumour cells in BALB/c Nu-Nu, athymic mice.[35] Each set containing ten mice receives an oral dose of 5% blueberry powder; the other batch is fed the AIN 96G diet, and after fourteen days, MDA-MB-231-luc-D3H2LN is introduced into both groups' mammary fat pads through orthotropic injection.

To calculate the tumour volume, the tumour volume is compared in mice given 5% blueberries, 10% blueberries, and mice on the AIN93 D diet. The control mice have lower tumour volumes in weeks five and six. When they are given 5% blueberries, in week six, the tumour volume is lowered in comparison to the control mice given this 5% blueberry diet. There is also a 70% lower liver metastasis and a 25% decreased lymph node metastasis on comparison with control mice.[36] Leukotriene B4 receptors are present in inflammatory cells such as neutrophils macrophage T- cells and eosinophils.[37] These levels of leukotriene B4 receptors will be increased in cancers this leukotriene b4 promotes metastasis[38] in both the 5% and10% blueberry diet there was an increased adenomatous polyposis coli protein this protein degrades beta catenation the powerful oncogenic transcription factor responsible cell differentiation[39] and increase in caspases level result in apoptosis of MDA-MB-231 cell.

Combating Cyclophosphamide-Induced Lung Toxicity with Blueberries

The most often used medication for immunosuppressive, anti-cancer, and other treatments is cyclophosphamide. Cyclophosphamide is metabolised by the microsomal cytochrome P450 in the liver with two active metabolites phosphor amide mustard and acrolein. The acrolein interacts with the tissue's anti-oxidant Défense mechanism and induces the reactive oxygen species that damage the mammalian cells leading to toxicity of multiple organs. Lung damage with cyclophosphamide can range from pulmonary fibrosis to interstitial pneumonia. The effects of blueberry anthocyanin-enriched extracts on lung damage caused by cyclophosphamide were investigated. A 220g Sprague-Dawley rat was utilized in this

experiment. Four groups of rats were randomly assigned: one for the vehicle control, one for cyclophosphamide treatment, and two groups with BAE treatment (20 mg/kg and 80 mg/kg). Rats in the groups treated with blueberry anthocyanin extract plus cyclophosphamide received intraperitoneal injections of 100 mg/kg of the drug after 7 days of BAE treatment. An equivalent volume of saline was intraperitoneally injected into the rats in the vehicle group. Following the experiment, samples of the lung and blood were obtained for testing. Bronchoalveolar fluid (BALF) was collected and the lungs were weighed on the assay side. After immediately centrifuging the fluid for 20 minutes at 300 g, the total cell count was determined. Using bovine serum albumin as the reference protein, the protein concentration was ascertained. Protein concentration in the fluid divided by plasma concentration was used to indicate pulmonary permeability. Tumor necrosis factor and interleukin 1 and 10 were measured using ELISA kits to identify the cytokines in the supernatant. To ascertain the protein concentration, the right lung was homogenized and the supernatant was collected. Myeloperoxidase, superoxide dismutase and malondialdehyde concentrations were quantified.

The outcome demonstrates that, in a typical state, the vehicle group's breathing is normal. However, there was coughing, noticeable polypnea, dullness, fluffing, and withering of the fur in the cyclophosphamide control group. In Blueberry anthocyanin extract administered groups, this appearance has slightly improved. In the 80mg/kg BAE groups, there was a reduction in oedema and congestion. The cyclophosphamide-induced group has severe lung damage with pulmonary oedema, haemorrhage, and cellular inflammatory infiltrates; the vehicle group is uninjured. This analysis demonstrates that the cyclophosphamide toxicity was reduced by the blueberry anthocyanin extract, particularly at 80 mg/kg. In the cyclophosphamide group, ten times more polymorphonuclear neutrophils were found in the bronchoalveolar fluid; however, in the blueberry extract group, these two parameters were lower than in the cyclophosphamide group, especially in the 80mg/Kg group. In the cyclophosphamide control group, there was a decrease in the levels of the tight junction protein-1 and claudin-4 this indicates the high permeability of the lungs since Reduced expression of tight junction proteins has been identified as a major factor in numerous increased permeability epithelial/endothelial lesions. However, the group that used blueberry extract stopped the decline in claudin-4 and tight junction protein-1 levels which indicates the anti-inflammatory action of the blueberry extract. Additionally, the Blueberry extract group lowers the malondialdehyde and Myeloperoxidase levels. The primary enzyme produced by

Polymorphonuclear neutrophils leukocytes, myeloperoxidase, is linked to the level of neutrophil infiltration in specific tissues. Since it can cause the conversion of ferritin to free Ferrous ions, which exacerbates oxidative damage, it is also a generator of ROS. Along with the improvement of Superoxide dismutase, which are non-enzymatic anti-oxidants, it indicates the antioxidant activity of the Blueberry extract. By this study, we could conclude that Blueberry anthocyanin extract attenuates cyclophosphamide-induced lung toxicity, anti-oxidant, and anti-inflammatory and suppresses the lysosomal protease characteristics that may involved in the protective roles of Blueberry anthocyanin extract against Cyclophosphamide lung toxicity.[40]

Anti-diabetic property of blueberry extract by activated AMPK pathway

Diabetes mellitus is an ametabolic disorder where blood glucose levels are elevated. Diabetes mellitus is of type 1 and type 2. Type 1 is caused by the destruction of beta cells present in islets of Langerhans. This destruction is due to an autoimmune disorder. Type 2 diabetes is mainly due to insulin resistance of cells.[41] In type 2 diabetes, insulin receptor functions are lowered.[42] Some studies show that blueberry extract has a significant hypoglycaemic effect on type 2 diabetes .C57BL/6J male mice of 20 g were maintained at a temperature of 25 degrees Celsius for the experiment. Streptozotocin was dissolved in sodium citrate buffer solution and administered intraperitoneally after a 12-hour fast, four weeks later.

Streptozotocin along with a HFD induces type 2 diabetes in male mice. Mice have type 2 diabetes mellitus were found after 1 week of streptozotocin induction by blood glucose test after fasting overnight. The mice with diabetes are given a low dose of blueberry anthocyanin extract 100mg/kg, high dose of blueberry anthocyanin extract400mg/kg, Some diabetic mice, referred to as model mice, receive 100 µl of solvent instead of blueberry extract.

All these diets are given continuously for six days. On the seventh day, fasting blood glucose level was tested and it was found that model mice had higher fasting blood glucose than the control mice and all these processes continued for 5 weeks. At the end of the fifth week, it was found that the diabetic mice given a low and high dose of blueberry anthocyanin extracts had low blood glucose levels. After killing the mice, organs are weighed and we can find that there is a difference in the weight of the organs. The mice given low and high doses of blueberry anthocyanin extract have lower body weight than the control mice. In the fifth week, it was also declared that the level of AMPK was greater in mice given low and high doses of blueberry anthocyanin extract.[43] AMPK is a heteromeric. AMP allosterically

united to a gamma subunit of protein kinase.[44] Activation of AMPK leads to phosphorylation of acetyl CoA carboxylase and inhibits fatty acid production. AMPK stimulates GLUT 4, an insulin-dependent protein through which glucose is taken by the cell; it also inhibits gluconeogenesis.[45] This study demonstrated the blueberry anthocyanin extract's ability to prevent type 2 diabetes.

The impact of blueberry anthocyanin on ARPE-cells in high glucose conditions REDD1/GSK3 beta pathway

The most prevalent kind of diabetes, diabetic retinopathy, impairs eyesight in senior citizens and those in their milder years. The retinal pigment epithelium functions as both a photoreceptor regulator and a selective barrier. The retinal pigment epithelium may be harmed by the elevated glucose levels. One function of the epithelium is to slow down the onset and advancement of diabetic retinopathy. The therapeutic effects of blueberry anthocyanin extracts (BAE), in particular the antioxidant cyanidin 3-o-glucoside, against retinal pigment epithelium cell damage are the main focus of this work. The primary causative cause for the development of diabetic retinopathy is hyperglycaemia. Hyperglycaemia causes aberrant metabolism, the production of ROS, and damage to several cell types in the retinal layer.

In the hyperglycemia-induced ARPE-19 cell model, an increase in the ROS and dysfunction of cells was observed. This creates an imbalance of cell homeostasis. Regulated in the development and DNA damage 1[REED-1], which is vital in controlling oxidative stress and has been intimately linked to the cellular stress response. Next, they administered Cyanidin 3-o-glucoside riced blueberry extract to the APRE-19 cell model, which showed lower expression of Regulated in the development and DNA damage -1 protein and reduced the oxidative stress in the cell lining. This could be explained due to the antioxidant activity of the extract. Overall, the study provides an idea about the therapeutic effect of cyanidin 3-o-glycoside present in the blueberry extract against diabetic retinopathy.[46]

***The impact of the blueberry phenolic extract on gut bacteria composition in* C57BL/mice**

Xinyao Jiao and colleagues' work published in "The Journal of Nutritional Biochemistry" looks into how the polyphenol content of blueberry extract affects the gut microbe in mice fed a high-fat diet as well as how the gut microbe is regulated in obesity. Four-week-old C57BL/6J mice were split into four groups for this 12-week study, with Group A receiving a

Normal Fat Diet. Group B was given a high-fat diet, Group C had a high-fat diet plus 200 mg/kg of blueberry polyphenol extract, and Group D, who is regarded as the positive control group, received a high-fat diet plus orlistat. In all of these groups, the mice had free access to food and water. The food intake and weight of the mice were measured twice a week for 12 weeks. At the end of this experiment, the faecal samples were collected and stored at -80 degrees Celsius. Blood samples were collected by cardiac puncture and were centrifuged for serum analysis. After the sacrifice of the mice, the liver, Epididymal White Adipose Tissue, heart, kidney, spleen, pancreas, brain and Brown Adipose Tissue were stored in liquid nitrogen at negative eighty degrees Celsius. Total cholesterol, Triglycerides, High-Density Lipoprotein Cholesterol, low-density Lipoprotein Cholesterol, AST and ALT were determined. Hepatic and Faecal lipids were extracted using the Modified folch method for the analysis of Total cholesterol and Triglycerides. The liver and Epididymal White Adipose Tissue protein expression of P-AMPK and AMPK were examined using western blotting. Last, the gut microbe analysis was done by 16s rRNA gene sequencing to study the differences and changes in the gut microbe among the groups. Upon completion of the analysis, it appears that the group fed a high-density feed had a higher body weight than the group fed a normal fat diet. The Blueberry Extract High-Fat Diet group had a lower body weight than the High-Fat Diet group, but not a lower body weight than the Normal group. It was noticed that the food intake of the High-fat diet+ blueberry extract group was higher than the Normal Fat Diet but significantly lower than the High-fat diet-only group. Compared to the group that received orlistat, the blueberry extract group's liver, white adipose tissue, and brown adipose tissue weights were lower, but not significantly. In the serum analysis, it was found that the Total cholesterol, triglyceride, Lipoprotein Cholesterol, Aspartate aminotransferase, Alanine transaminase and leptin were high High-fat diet group but were less in the Polyphenol extract group. High-density lipoprotein Cholesterol was low in the High-fat diet but high in the Polyphenol extract group, which indicates its anti-obesity properties and cardioprotective properties. The Total cholesterol and Triglycerides in the faecal are less in blueberry Polyphenol extract, especially Triglycerides in the liver were much less in the Polyphenol extract group than in the Normal Fat Diet mice group. The Polyphenol extract and orlistat showed down-regulation of FAS, PPARγ that contracts that of the High-fat diet -only administered group.

Speaking about the gut microbial analysis High-fat diet group is high in *Firmicutes* and *Actinobacteria*, a low level of *Spirochates* and extremely low in *Cyanobacteria* and

Tenericutes than the Normal diet group. The Polyphenol extract-administered group showed high levels of Proteobacteria and low in Actinobacteria. At the genus level, the High-fat diet group is richer in Allobacullum and Coprobacillus than the Polyphenol extract group and has low levels of Lactobacillus, streptococcus and other bacteria as well. In the Polyphenol extract group a high level of Helicobacter with a lower level of *prevotella* than in the High-fat diet group. The high *Bifidobacterium* genus indicates the good probiotic effect of the extract since it is a good probiotic that shows a good increase in number when probiotics are given. At the same time, it also shows fewer numbers of bacteria genera like lactobacillus and others as well which indicates the extract is specific for specific bacteria. Through Redundancy, analysis suggests that the High-fat diet + Polyphenol extract and High-fat diet with Orlistat groups have similar micro gut environments. Overall, the study shows that blueberry Polyphenol extract leads to less Brown Adipose Tissue, Epididymal White Adipose Tissue and a high number of High-Density Lipoprotein Cholesterol, which indicates its anti-obesity properties. In addition, the extract is very specific about specific bacteria and enriches the gut microbe hence working against obesity. Studies show that gut bacteria work by inhibiting insulin-mediated fat accumulation by producing SCFA also known as Short Chain Fatty Acid. Also, gut microbes work by regulating lipids by regulating AMPK and so on.[47]

A comprehensive look at the antimicrobial effects and membrane damage of *vibrio parahaemolyticus* by blueberry extract

This study focuses on the antibacterial properties of blueberries and their capacity to damage *Vibrio parahaemolyticus*. Gram-negative *Vibrio parahaemolyticus* bacteria have a thicker lipid bilayer than their positive counterparts. It has been identified as an oceanic disease that affects fisheries since it usually infects fish, shellfish, zooplankton, and other aquatic commodities. Consuming raw fish is one of the main reasons. V. parahaemolyticus possesses several virulence factors, such as adhesiveness, thermostable direct hemolysin (TDH), TDH-related hemolysin (TRH), Type 3 secretion system, and TRH, which excrete proteins directly into the host body. Currently, it may be deadly and lead to minor intestinal infections such as gastroenteritis, a condition marked by fever, spasms, bloating, nausea, purging and additionally sepsis.

Usually, the diseases caused by *Vibrio parahaemolyticus* were managed by antibiotics, however, are no longer effective in curing bacterial infections due to antibiotic-resistant bacteria. As a result, researchers are exploring natural alternatives to antibiotics. In this study,

blueberry was used to estimate its ability against the bacteria. Here, the least inhibitory concentration of the blueberry extract and the minimum bacterial concentration were determined against three strains of V. paraheamolyticus, ATCC 33847, F 13, and ATCC 17802. The findings were in the order 25, 25, and 12.5 mg/ml, while the Minimum bacterial concentration ranges were 50, 50, and 25 mg/ml. This indicates that blueberries are efficient against this. Overall, antibacterial properties cause it to weaken the integrity of its cell walls and prevent the expression of seven membrane genes, inhibiting the development of bacteria; however, the precise process is still unknown. This concludes the anti-microbial effect of the blueberry against Vibrio *parahaemolyticus* and suggests for further research.[48]

Exploring the impact of anthocyanin on retinal oxidative stress and inflammation through nrf2/ho-1 signalling

Blueberries are high in anthocyanin, which offers considerable protection against a variety of chronic illnesses. Several recent studies have demonstrated the antioxidant, anti-inflammatory, and neuroprotective qualities of blueberry anthocyanins. Researchers have found that blueberry anthocyanins (BAs) have an effect on inflammation and oxidative stress in the diabetic retinal cells of rats. They applied their greatest outcomes, which they obtained to diabetic retinopathy. Long-term increased blood glucose levels are the cause of diabetic retinopathy, one of the most common forms of diabetic retinopathy in the world. Prolonged increased glucose levels have been associated with neovascular glaucoma, diabetic macular oedema, vitreous haemorrhages and ultimately blindness. Recent research has demonstrated that the pathophysiology of diabetic retinopathy involves both chronic inflammation and oxidative stress.

For the experiment, male rats were selected and split into five groups. The remaining four models were given intraperitoneal injections of streptozotocin (STZ, 60 mg/kg) to develop diabetes, whereas the control group was given simply saline water. One group was left untreated, and the other groups received oral doses of blueberry extract (20, 40, and 80 mg/kg) for 12 weeks. Numerous immunoregulatory molecules known as anti-inflammatory cytokines, which lower inflammation and increase levels in the diabetic-induced retina, as well as VEGF and interleukin-1β (IL-1β), which are also significantly upregulated in diabetic retinopathy and signify oxidative stress, are also present. VEGF over-expression refers to the formation of new, aberrant blood vessels. In the Blueberry extraction groups it was noted that by raising glutathione and glutathione peroxidase activity levels and lowering reactive oxygen species

(ROS) and malondialdehyde levels, Blueberry anthocyanin extracts enhanced the retina's antioxidant capacity. Additionally, the extract increased nuclear factor erythroid 2-related factor 2 mRNA and Heme Oxygenase-1 protein levels. Blueberry extracts work against inflammation in many ways, out of which one way was found they inhibited the synthesis of pro-inflammatory molecules and stopped oxidative stress. According to these results, blueberry extract may protect retinal cells from oxidative damage and inflammation caused by diabetes via modulating Nrf2/HO-1 signalling.

The research concludes the effect of blueberry extract on diabetic retinopathy by reducing oxidative stress and inflammatory molecules in the in-vivo studies.[49]

5. ADVERSE EFFECTS

Despite being widely regarded as a healthful fruit, blueberries may result in digestive problems like diarrhoea or constipation. An overabundance of blueberries can cause cramps or pain in your stomach. Consume blueberries sparingly and be sure to stay hydrated to prevent these kinds of issues.[50] Blueberry cannot be consumed by people with Glucose-6-phosphate dehydrogenase (G6PD) deficiency.[51] For the majority of people, blueberry supplements seem to be safe. Still, given that the supplements may drop blood sugar levels, patients with diabetes should speak with their doctor before consuming blueberry-based supplements.[52] In addition, blueberries are frequently to blame, for resulting stains on teeth as per the American Dental Association (ADA).[53] Oxalates are also abundant in blueberries. Eating an excessive amount of blueberries can make kidney stones worse for people who are prone to them.[54] Salicylates prevent blood clotting so it is dangerous to consume blueberries during bleeding.[55]

6. MARKETED FORMULATION

Due to the high content of vitamin K and vitamin C in blueberries, the majority of products on the market are meant to be used as supplements. A lot of skincare products and facemasks contain blueberry extracts because of their antioxidant qualities.

Table 2: marketed products of blueberry.

NAME OF THE PRODUCT	BRAND NAME	PRICE (₹)
500 mcg biotin blueberry gummies	PURNA GUMMIES	99[56]
Blueberry extract powder	HERBA DIET	1,076.99[57]
Blueberry facial kit with blueberry extract	SKIN SECRETS INDIA	1,240[58]
Fresh Start Oil Clear Face Wash Blueberry	HIMALAYA WELLNESS	160 [59]

Urban platter blueberry syrup	URBAN PLATER	494 [60]
Blueberry liquid extract	YOUNG CHEMIST	249 [61]
Vitamin Blue Berry Vegetarian Capsule	VITAWIN	549 [62]
Wild blueberry & Pomegranate veggie caps	IHERB	1,073[63]
Super-rich blueberry concentrate	IHERB	1192 [64]
Sirona Blueberry Hydrating Body Lotion	SIRONA	349 [65]

7. HOME MADE REMEDIES

Due to the unique qualities of blueberries, there are effective home treatments like

- Blueberry face mask
- Blueberry syrup
- Blue berry water
- Dried blueberries
- Lacto-fermented Blueberry jam

Preparation of Blueberry face mask

Ingredients

1. 1 tablespoon of oatmeal or oat flour
2. 5-6 fresh blueberries
3. 1 tablespoon raw honey

Preparation

If using oat flour, omit this step and just blend the oatmeal. Mix the honey into the mashed blueberries until they become soft or juicy. After that, incorporate this with the blended oat flour or meal and stir.[66]

Treatment

Blueberries are known to contain antioxidants and a variety of phytochemicals that can be used to treat skin conditions. Research has shown that applying this substance topically helps to prevent acne, wrinkles, and skin problems caused by UV radiation. The oxidative stress and UV-induced skin inflammation are lessened by the presence of phytonutrients and extracts, which also prevent keratinocyte migration and proliferation generated by ozone. Reduced nuclear factor Kappa B activation and prevention of collagen degradation are observed. UV radiation breaks down skin proteins including involucrin and filaggrin, which results in a loss of barrier function and the development of chronic inflammation of the skin. These proteins' level is raised by the blueberry extract, which also provides UV protection.[67]

Preparation of blueberry syrup

Ingredients

1. Sugar
2. Cornstarch
3. Lemon juice
4. Fresh blueberries

Preparation

Add the cornstarch, water, sugar, and lemon to a medium container and whisk until blended. When the mixture reaches a boil, stir in the blueberries then add the blueberries. Simmer for 4–5 minutes, or until the syrup thickens, then let cool.[68]

Treatment

Anthocyanins and antioxidant activity found in blueberries are abundant and exhibit anti-cancer and blood sugar-regulating properties. The blueberries are slowing the growth of cancer cells and speeding up their demise. According to a study (Minker C et al. 2015), colon cells are killed in lines by blueberries because they contain the antioxidant proanthocyanidins. According to a 2017 study by Lin et al. on animals, blueberries inhibit ovarian cancer cells by reducing the growth of tumours and regulating certain enzymes. According to a 2014 Jennings et al. study, blueberries reduce insulin resistance.[69]

Preparation of blueberry water Ingredients

1. 1 cup of fresh blueberries
2. 1 medium lemon
3. 8-10 cups of water
4. 1-2 leaves fresh mint (optional)

Preparations

Once cleaned, lightly crush the blueberries to release the juice. Segment the lemon into small pieces. Squeeze the lemon slices into ten glasses of water and mix with the crushed blueberries. Keep the mixture chilled so that it can absorb the flavours.[70]

Treatment

Considered the epitome of antioxidant foods are blueberries. Numerous studies show that it decreases blood sugar, improves memory, lessens heart disease, and increases brain

functionality. Antioxidants are substances that shield cells from the harm that free radicals and illnesses like cancer can cause. Parkinson's and Alzheimer's illnesses.[71]

Preparation of dried blueberries

Ingredients

1. 600 grams of blueberries.[72]

Preparation

Pierce each fruit twice, pushing the types through. Put the food dehydrator racks together. After 8 to 9 hours of heating to a temperature of about 55 to 60 degrees Celsius, flip the blueberries, and continue heating for an additional 30 to 34 hours before letting them cool.[72]

Treatment

An anti-obesity chemical is found in dried blueberries. The fermented blueberry-alcohol beverages' anthocyanins can prevent adipocytes from signalling insulin. Polysaccharides from the blueberry suppress tumour growth, and the polyphenols from the berries have an effect in inhibiting adipogenesis. According to this research, blueberries provide top-notch immune benefits.[73]

Preparation of lacto-fermented blueberry jam Ingredients

1. Blueberry
2. Lemon juice
3. Sugar

Preparation

Put all of the blueberries and sweetness in a vessel and cook for five minutes, then mash them to release the juice. Once the temperature drops and the whey is added, let it cool to room temperature. Move to the sanitized jar and set it aside for two days. If too much gas builds up, burp it and place it in a cold place to store.[74]

TREATMENT

The ability of lacto-fermented blueberry juice to decrease cholesterol in vitro was investigated. This results in a rich probiotic, pH variations, antioxidant characteristics that support cell survival, and a decrease in cholesterol in vitro. According to this study, the best probiotics for blueberry fermentation are Lactobacillus plantarum DB-2, Lactobacillus fermentum J-1, and Lactobacillus plantarum SK-3. This suggests that the jam that is best for

your health is fermented blueberry jam.[75]

CONCLUSION

The health advantages of blueberries have been the subject of current research, as covered in this article. It is known that blueberries are high in anthocyanin in addition to their phytochemical components. According to the studies covered in this article, blueberry extracts may be beneficial to the body for a variety of pathological diseases. The effects of anthocyanin, which is plentiful in blueberry fruits, should be further studied in light of both their negative consequences and positive health effects.

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