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Abstract:

This study aimed to investigate the effects of black plum (Prunus salicina) and black cherry (Prunus cerasus) juices in alleviating multiple sclerosis (MS)-related complications in rats. The two fruits' total phenolics, flavonoids, anthocyanins, and ascorbic acid contents were determined, along with the antioxidant activity of the juices in vitro. In the animal experiment, thirty adult male albino rats (weighing 130 ± 5 g) were used, Six of these rats served as a normal control group and continued on a baseline diet. The remaining rats were administered cuprizone (3 g/kg of diet) to induce a condition similar to multiple sclerosis and were divided into four groups. One group acted as a positive control, while the other three groups received a daily dose of juice at a volume of 15 ml/kg body weight via a stomach tube. One group was given black plum juice, another received black cherry juice, and the third received a mixture of both juices (1:1 v/v). At the end of the experiment (6 weeks), blood samples were collected for analysis. Results showed that the inflammation markers (CRP, COX-2, IL-12, TNF-α) significantly increased in the positive control group but decreased significantly in the groups treated with the juices. Immunoglobulin levels (IgG and IgM) decreased in the positive control group. However, treatments with black cherry and the mixture of juices significantly improved the levels of both IgG and IgM. Regarding oxidative stress markers, the positive control group showed a significant increase in malondialdehyde (MDA) levels and a decrease in total antioxidant capacity (TAC) compared to the normal control. Conversely, the groups treated with the juices exhibited

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reduced MDA levels and increased TAC levels compared to the positive control. The antioxidant and anti-inflammatory activities of black plum and black cherry juices, make them recommended for patients with multiple sclerosis.

Keywords: Multiple sclerosis, black plum, black cherry, total phenols- flavonoids, anthocyanins, antioxidant, inflammation, rats.

1. Introduction

Neurological diseases pose a significant public health challenge, particularly for the elderly population. According to the latest report from Rotterdam, it is estimated that one in three men and one in five women will experience dementia, a stroke, or Parkinson's disease during their lifetime (Licher et al., 2019).

Multiple sclerosis (MS) is a continual inflammatory sickness of the central nervous system (CNS) affecting white and grey matter. Inflammation and oxidative stress are also accompanied by MS. Multiple sclerosis sufferers confirmed a multiplied cardiovascular (CV) danger associated with impaired autonomic control of cardiovascular functions. However, the underlying molecular mechanisms are not elucidated (Akyuz and Villa, 2020).

Tauheed et al. (2016) reported that Multiple sclerosis (MS) is caused by chronic inflammation in the central nervous system (CNS). This disease affects components of the central nervous system, such as white and grey matter, when nerve tissues are constantly exposed to inflammation and oxidative stress leads to severe damage, and this is evident in multiple sclerosis. The adverse outcome of an imbalance between the body's antioxidant defence system and the rampaging effects of reactive species is referred to as oxidative stress. It has been linked to the pathogenetic mechanisms of several diseases, including neurodegenerative diseases (Alzheimer's and Parkinson's disease), inflammatory diseases, and cancer (Egbuna and Ifemeje, 2017). Bali and Kasman (2020) reported that inflammatory particles are pleiotropic protein complexes that play a major role in the pathophysiology of MS. Because there is a link between inflammasome activation and multiple sclerosis, targeted suppression of inflammatory bodies may thereby diminish inflammatory processes and improve functional remyelination.

Jhelum et al. (2020) found that cuprizone has been used to demyelinate, which is similar to what occurs in MS, where it induces rapid loss of oligodendrocytes by ferroptosis. Oxidation of lipids by iron and loss of oligodendrocytes (by iron cell inflammation), this rapid storage of iron in cellular stores also leads to cell death in other neurological diseases. Cuprizone-induced toxicity has been reported to cause memory impairment, weight loss, impairment in exploratory drive and increased oxidative stress. It is a neurotoxicant causing neurodegeneration through enzyme inhibition and oxidative stress (Omotoso et al., 2019). In a study conducted by Elbadrawy et al. (2022), it was found that the juices of black plum and black cherry significantly improved lipid profile, as well as liver and kidney functions, in experimental rats injured with multiple sclerosis.

Flavonoids also known as bioflavonoids, include flavanols, flavones, flavanones, antioxidants, isoflavones, anthocyanidins, and chalcone due to their chemical structure. These compounds play an important role in the management of MS because they possess antioxidant properties, which can reduce cytokines as well as inflammatory inducers as they are considered cellular markers involved in the inflammatory process such as interleukin and tumor necrosis factor-alpha (Karak, 2019). Li et al. (2021) reported that anthocyanins are considered a protective factor against neurological diseases, as they reduce the incidence of functional disorders of nerves such as cognitive and memory impairment, through their ability to support and protect neurons and glial cells and contribute to reduce oxidative stress and responses resulting from inflammatory process, in addition to its ability to stimulate the production of glutamine. Flavonoids are a class of plant-derived dietary polyphenols that have been known for their precognitive and anti-inflammatory effects, they are characterized as antioxidants. Flavonoids are now believed to act directly on neurons and glia via the interaction with major signal transduction cascades, as well as indirectly via interaction with the blood-brain barrier and cerebral vasculature. (Jaeger et al., 2018). Igwe and Charlton (2016) mentioned that plums have high phenolic content, mostly anthocyanins and natural antioxidants so they play a role as anti-inflammatory, antioxidant and memory improvement. Recently, the peel of the Black plum fruit has been recognized as a natural and cost-effective source of antioxidants. It plays a role in preventing degenerative diseases by scavenging free radicals and reducing conditions associated with abnormally high levels of reactive oxygen species (ROS) in the body (Traore et al., 2020). Black cherry, like most fruits, is rich in antioxidants and minerals. It has a wide range of total phenolic chemicals, including flavonoids and tannins (Amarowicz and Pegg, 2019). Sweet cherries contain dietary phenolic components such as phenolic acids (hydroxycinnamic acids) and flavonoids (anthocyanins, flavan-3-oles, and flavonols), both of which boost overall health and help to avoid many chronic diseases linked to oxidative stress (Girelli et al., 2016; Picariello et al., 2016). Therefore, this work aims to study the effect of black plum and black cherry intake in alleviating the side effects of multiple sclerosis through their roles in preventing oxidation, inflammations, and neurodegeneration.

2. MATERIALS AND METHODS

2.1. Materials

Fruits: Black plum (Prunus salicina) and Black Cherry (prunus cerasus) were purchased from the local market in Mansoura City.

Chemicals: All the used kits and chemicals of analytical grade were purchased from Al-Gomhorya Company for Trading Medicines and Medical equipment, Mansoura, Egypt and Cuprizone powder was obtained from Lab Chemical Company, Egypt

Diet: A standard diet of fine ingredients was prepared according to NRC (1995).

Animals: Thirty adult male albino rats (weighing 130 ±5 g), were obtained from Helwan farm of experimental animals, Cairo, Egypt. (Guidelines for ethical conduct in the care and use of animals in research were obtained from the Scientific Research Ethics Committee of Mansoura University).

2.2. Methods

2.2.1. Black plum and Black cherry juice preparation: The fruits were washed three times with tap water, dried with blotting paper, and then stored under freezing until use. After that, the fruits were squeezed in the blender to reach the appropriate consistency which was given via the stomach tube with a dose of 15 ml/kg body weight **(Elbadrawy and Elkewawy, 2019)**.

2.2.2. Estimation of anthocyanin, and ascorbic acid (Vit C) of black plum and black cherry

Anthocyanins were analyzed using the methods described by Mancinelli (1984).

An ascorbic acid (Vitamin C) assay was carried out as described by Sadasivam and Balasubramanian (1987).

2.2.3. Determination of total polyphenol and flavonoid content of black plum and black cherry. The total polyphenol content was estimated using the Folin–Ciocalteu reagent as reported by Limmongkon et al. (2017). The total flavonoid content was determined by a colorimetric method using aluminium chloride with some modifications as described by Munhoz et al. (2014).

2.2.4. Antioxidant activity:

* Determination of free radical scavenging activity of black plum and black cherry:

It was determined by using 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical according to the method of Dasgupta et al. (2016).

*Reducing power assay {FRAP (ferric reducing antioxidant power) assay}

The reducing power of the tested samples was assessed according to Debnath et al. (2011),

2.2.5. Biological assays:

Experimental design: The thirty adult male rats used in this experiment were housed in metallic cages under healthy environmental conditions for acclimatization. Water and diet were provided ad libitum. They were divided into 5 groups (6 rats each), one of them remained on the basal diet only which served as normal control. The remaining groups were treated with cuprizone in a dose of 3 g / kg diet (Buonvicino et al., 2021). One of these four groups was left as a positive control (MS control). The other three groups were treated separately with the juices of black plum, black cherry, and their mixture (1:1 v/v) in a dose of 15 ml/kg b.wt using a stomach tube from the first day to the end of the experiment (6 weeks). At the end of the experiment, all the rats were sacrificed, their blood was drawn from the portal vein and their plasma was separated. Brains, sciatic and optic nerves from each rat were collected, immersed in 10 % formalin as a fixative, and then sent to the pathology department of Veterinary Medicine College, Mansoura University for histopathological examination.

Biochemical analysis:

- Examination of Total antioxidant capacity(TAC) was determined by the method of Koracevic et al. (2001).
- Malondialdehyde (MDA) was determined by the method described by Stocks and Donnandy (1971).
- Immunoglobulin G (IgG) and Immunoglobulin M (IgM) were performed according to Silva et al. (1984).
- C-reactive protein (CRP) concentration in the serum was estimated according to Friedman and Young (2001).
- Cyclooxygenase-2 (COX-2) was determined according to Kulmacz and Lands (1983).
- Interleukin-12 (IL-12) was assessed according to Raetska et al. (2017).
- Tumor necrosis factor (TNF-α) was investigated according to Brouckaert et al. (1993).

2.2.6. Histopathological examination:

Fixed samples from the brain, sciatic nerve, and optic nerve in 10 % neutral buffered formalin were flushed in xylol and embedded in paraffin. 4-5 µm thick sections were prepared and stained with hematoxylin and Eosin (H&E) for subsequent histopathological examination (Bancroft et al., 1996).

2.2.7. Statistical analysis:

The results were statically analyzed by using a computer program (SPSS); one-way analysis of variance (ANOVA) was carried out, and the difference was considered significant at P-value < 0.05.

3. Results and Discussion:

3.1. Total phenols, flavonoids, anthocyanins and ascorbic acid of black plum and black cherry juices:

The results in Table (1) revealed that the total phenols of black plum and black cherry were 317 and 292 mg GAE/100g, respectively, where their content of flavonoids was 85.03 and 74.2 mg QE/100g, respectively. On the other hand, the anthocyanin content of black plum and black cherry was 55.6 and 56.2 mg /100g, respectively. Regarding the ascorbic acid content, it is clear that the black plum contains a higher amount (9.3 mg /100 g) than the black cherry (4.65 mg /100g). It is well known that plants' polyphenol compounds and ascorbic acid are essential in preventing oxidation in human body cells. So, they protect the body cells, especially the cell membrane and hence protect the body from diseases. Luna-Vázquez et al. (2013) found that the total phenolic level in black cherry was 362.2 mg of GAE/100 g and flavonoid levels were 201.8 mg of CE/100 g. Blando and Oomah (2019) found that ascorbic acid (vitamin C) generally ranges between 6-10 mg/100 g FW in sweet cherries. It was found that ascorbic acid (vitamin C) was 9.5 mg/ 100 g in fresh plums and 2.8 mg/ 100 g in plum juice (USDA, 2014).

Table (1): Total phenols, flavonoids, anthocyanins and ascorbic acid of black plum and black cherry juices (mg/100g on a wet weight basis).

Samples	Total phenols mg GAE/100g	Flavonoids mg QE/100g	Anthocyanin (mg/100g)	Ascorbic acid (mg /100g)
Black plum	317	85. 03	55.6	9.302
Black cherry	292	74.22	56.2	4.651

Each value is the mean of three replicates.

3.2. Antioxidant activity of black plum and black cherry:

3.2.1. DPPH assay

Free radical scavenging activity was performed by using DPPH radical. Free radicals are considered one of the causes of many diseases where they initiate many degenerative processes, which may cause damage to deoxyribonucleic acid (DNA), cell membranes and proteins. The assay of the DPPH radical depends on its maximum absorption at a wavelength of 517 nm. The color is converted to pale yellow in the presence of antioxidant substances. The reduction of the DPPH radical that occurred by the two fruit juices with different concentrations is recorded in Table (2). It was apparent from the results that the highest increase in the antioxidant activity of the two fruit juices was noticed with a concentration of 150 µg/mL with values of 56.19 and 52.01% for black plum and black cherry, respectively .The concentration of 100 µg/mL showed values of 50.23 and 49.8 % inhibition, whereas the lowest concentration of 50 µg/mL showed little activity. A small difference was noticed between the concentration of 150 and 100 µg /ml, so it is preferable to use the concentration of 100 µg/mL to save fruit juice. Consumption of foods, especially vegetables and fruits, which are rich in antioxidants, can prevent oxidative stress and protect the body from many diseases (Joshi et al., 2012). Imoisi et al. (2021) showed that the 50 % inhibitory concentration value of black plum fruit is defined as the actual concentration of the sample required to scavenge 50% of the DPPH free radical (IC50). Sweet cherry phenolic extracts have a high antioxidant potential, scavenging DPPH and inhibiting -glucose oxidase activity dependently (Gonçalves et al., 2017).

3.2.2. Reducing power:

Regarding the reducing power, it was noticed that the concentration of 400 µg /ml showed the highest reducing power. This means that the reducing power increases with increasing the juice concentration, although the two fruit juices have nearly good results with the low concentration. The half-maximal effective concentration (EC 50) was 549.41 and 568.65 µg /ml for black plum and cherry, respectively.

Table (2): Antioxidant activity of black plum and black cherry using DPPH assay and reducing power

Samples / Concentration µg/ml	Black plum	Black cherry
DPPH scavenging activity %		
50	45.12	42.24
100	50.23	49.80
150	56.19	52.01
Reducing power (OD)		
50	0. 169	0.210
100	0.218	0.230
200	0.280	0.274
400	0.361	0.366
EC_{50} µg/ml	549.41	568.65

Each value is the mean of three replicates.

3.3. Biological assays:

3.3.1. Effect of black plum and black cherry juices and their mixture on inflammation parameters in the serum of rats with MS.

The results in Table (3) showed that all the inflammation parameters, CRP, COX-2, IL-12, and TNF-α, increased significantly in the positive group, which received cuprizone only. This means the cuprizone drug caused severe inflammation in the cuprizone–induced MS rats .

C-reactive protein (CRP) is a marker of inflammatory diseases where it increases because of inflammation incidences. The results in Table (3) revealed significant decreases in the CRP levels in the groups treated with black plum, black cherry, and their mixture juices compared to the positive control, where their values were 1.62 ± 0.07, 1.63 ± 0.04, and 1.40 ± 0.02 mg /L, respectively, as compared to the positive group (2.05 ± 0.08 mg / L). The value of serum CRP in the mixture group reached nearly that of the normal control.

Regarding cyclooxygenase -2 (COX-2), which is an enzyme responsible for the conversion of arachidonic acid to prostaglandins, the findings in Table (3) showed that its value increased significantly in the positive control group, which was 8.2 ± 0.08 ng/ml as compared to the normal control (2.75 ± 0.13 ng/ml). On the other side, the MS groups which received the three juices under study revealed significant reductions in their serum COX-2 levels as being 5.35±0.07, 3.68±0.04, and 2.75±0.02 ng/ml for black plum, black cherry, and their mixture, respectively in comparing with the positive control (8.20±0.08 ng/ml). The highest decrease in the serum COX-2 level was observed in the group treated with the mixture juice, whose value was 2.75±0.02 ng. /ml, the same as the normal control value.

The juices of black plum and black cherry showed a significant decrease in serum COX-2 as the black cherry was better than the black plum in this respect compared to the positive control. The reduction in serum COX-2 levels was 66.46, 55.12, and 34.75 % for the mixture, black cherry, and black plum, respectively, compared to the positive control group.

On the other hand, Interleukin 12 (IL-12) is a cytokine that is produced by myeloid and other cell types, the findings in Table (3) showed that its value increased significantly in the positive control group which was 179.75 ± 12.0 pg/ml as compared to the normal control (33.10 ±4.04 pg/ml). On the other side, the MS groups which received the three juices under study revealed significant reductions in their serum IL-12 levels as being 76.6±0.54, 63.18±2,83, and 35.38±1.58 pg/ml for black plum, black cherry, and their mixture, respectively in comparing with the positive control (33.10±4.04 pg./ml). The highest decrease in the serum IL-12 level was observed in the group treated with the mixture juice where its value was 35.38±1.58 pg./ml which is similar to the normal control value .

It was noticed from the data in Table (3) that the value of serum TNF-α level of the positive group elevated significantly (559.25 ± 10.66 pg./ml) as compared to the normal control group (123.45 ± 3,76 pg. /ml). The three groups that received the three juices revealed significant decreases in their TNF-α levels compared to the positive group. The mixture juice group exhibited the best result where its value was reduced to nearly equal to that of the normal control. Both black cherry and black plum also significantly reduced the serum TNF-α level, but the black cherry was better than the black plum in this respect.

Table (3): Effect of black plum and black cherry juices and their mixture on inflammation parameters in the serum of rats with MS.

Parameters / Groups	CRP (mg/L)	COX_2 (ng/ml)	IL_12 (pg/ml)	TNF_α (pg/ml)
Normal Control	1.31±0.13[c]	2.75±0.13[d]	33.10±4.04[d]	123.45±3.76[d]
Positive Control	2.05±0.08[a]	8.20±0.08[a]	179.75±12.00[a]	559.25±10.66[a]
Black Plum	1.62±0.07[b]	5.35±0.07[b]	76.60±0.54[b]	263.78±0.17[b]
Black Cherry	1.63±0.04[b]	3.68±0.04[c]	63.18±2.83[c]	253.78±2.58[c]
The mixture of the two fruits	1.40±0.02[c]	2.75±0.02[d]	35.38±1.58[d]	127.30±0.77[d]

Each value is the mean ± SD

Mean values in each column with different superscripts are significantly different at $P \leq 0.05$.

Consequently, the data obtained indicated that the mixture of the two fruit juices produced significant results. The group that received this mixture showed notable reductions in blood levels of the four inflammation parameters compared to the positive control group. Inflammation may happen because of tissue injuries by abnormal stimuli such as exposure to mechanical, thermal, or chemical reactions. Inflammation is accompanied by the production of various cytokines and chemo attractant proteins from different sources such as the spinal cord (Stammers et al., 2012), the peripheral nerves (Zhang et al., 2007), cutaneous source (Dawes et al., 2014), the dorsal root ganglion (Siemionow et al., 2009), macrophages (including astrocytes and microglia) (Karthikeyan et al., 2016), mast cells

(Ito et al., 2015), endothelial cells (Stepanova et al., 2013), and Schwann cells (Qin et al., 2012).

Tumor necrosis factor-alpha (TNF-α) is an important cytokine detecting inflammatory pain. It is secreted by microglia under the influence of interferon-gamma (IFN-γ) during neuroinflammatory injuries

Samad et al. (2001) reported that glial cells could increase the production of prostaglandins (PGEs) through increased activation of cyclooxygenase (COX) enzymes in addition to their role in pro-inflammatory cytokines.

PGEs are also important in the case of pathological pain. Arachidonic acid is the precursor for prostaglandin G2 and H2 synthesis in a process which is catalyzed by COX enzymes (Fu et al., 1999)

Mulabagal et al. (2009) reported that the anthocyanins of sweet cherry in the concentration of 250 μg/mL inhibited COX enzymes by 80–95%. They stated that the inhibition of COX-2 was more than what happened to COX-1.

Spuler et al. (1996) found that one of TNF's tasks is to stimulate cytokines, chemokines, mononuclear cells, and adhesion cells. In MS patients, TNF-α increased, as are other cytokines, which shows a good connection with disease progression.

CRP is an acute-phase protein produced by hepatocytes in response to cytokines in the inflammatory response. In cases of acute inflammation, its serum level rises; however, it is known to be linked to chronic inflammation (Luan and Yao, 2018). Its concentration increases during the inflammatory process, which directly plays a direct role. Spagnuolo et al. (2017) reported that neuroinflammation is tightly linked to the aetiology of neurodegenerative illnesses. Its most prominent feature is microglial activation in the CNS, which causes inflammatory processes and gradual neuronal cell death by producing pro-inflammatory cytokines intake of cherries (280 g/day) has been shown to lower levels of plasma urate, C-reactive protein, and NO in 10 healthy women while having no effect on plasma albumin or tumor necrosis factor (Jacob et al., 2003).

Tart cherry anthocyanins have cyclooxygenase inhibitory properties comparable to commercial anti-inflammatory medicines like ibuprofen and naproxen (Mulabagal et al., 2009). In rat microglial cells, tart cherry (cv Montmorency) treatment lowered inflammatory and oxidative stress signalling by reducing NO, TNF-, and COX-2 levels in a dose- and time-dependent manner (Shukitt-Hale et al., 2016).

Tart cherry intake and cherry anthocyanins have been linked to reduced inflammation and inflammatory-related disorders in some animal and human studies. Tart cherry intake and cherry anthocyanins have been linked to reduced inflammation and inflammatory-related disorders in many animal and human studies (Traustadottir et al., 2009; Mulabagal et al. (2009) and Seymour et al. (2009) found that inflammation indicators in rats were lowered by up to 50% in response to a cherry-enriched diet.

Some studies looked at the effect of phenolics and anthocyanins of cherry (sweet and sour) on the viability of neuronal cells exposed to oxidative stress. The findings revealed that cherry phenolics protect neuronal cells from cell-damaging oxidative stress in a dose-dependent manner (Kim et al., 2005; Fornasaro et al., 2016).

Carvalho et al. (2015) reported that anthocyanins have been employed as a co-adjuvant to avoid pathological conditions and neurodegenerative illnesses in the pons of rats simulating multiple sclerosis demyelination. They inhibit peripheral immune cell migration and regulate the inflammatory response by lowering the synthesis of pro-inflammatory cytokines like IL-1 and TNF- α and increasing the production of anti-inflammatory cytokines like IL-10.

3.3.2. Effect of black plum and black cherry juices and their mixture on blood Immunoglobulins and oxidative stress in multiple sclerosis rats.

Immunoglobulins play an essential role in the body's immune system. They are proteins synthesized in plasma cells to protect the body from foreign microorganisms such as bacteria and viruses or any other substances that the body recognizes as " non–self" antigens.

Immunoglobulin M (IgM) antibodies are produced as the body's first response to a new infection or a new non-self-antigen causing short–term production. They increase for several weeks and then decline as IgG production begins. About 70-80 % of the blood immunoglobulins are IgG. IgG antibodies are produced during an initial infection or other antigen exposure, rising a few weeks after it begins, then decreasing and stabilizing.

The results in Table (4) showed the effect of black plum and black cherry on immunoglobulins concentration in the blood in addition to their antioxidant activity. The results revealed that the values of IgG and IgM decreased significantly in the positive control group; this is because of rats' injury with cuprizone. On the other hand, the MS groups treated with the two fruits, or their mixture showed significant increases in the IgG content, while the black cherry and the mixture improved the level of IgM significantly as compared to the positive control. The best results were noticed in the mixture group, where there were significant increases in the IgG and IgM levels compared to the positive control. The level of plasma IgG of the mixture group reached that of the normal control, which means that the mixture juice has a potent immunity effect. The results indicated that the phytochemical content of the two fruits boosts the immune system, reflecting the improvement of the nervous system, which led to a decrease in MS disease.

Regarding the antioxidant activity of the MS groups which were treated with the fruit juices, malondialdehyde (MDA) and total antioxidant capacity (TAC) were measured, and their values are recorded in Table (4).

The results revealed that the concentration of blood MDA increased significantly in the positive control (57.9± 3.56 nmol /L). It was noticed that all the MS groups treated with the juices of the two fruits, or their mixture had significant decreases in their blood levels of MDA compared with the positive group. The best result in this respect was that of the MS group, which received a mixture of the two juices. Their blood MDA value was nearly the same as the normal control. On the other hand, the total antioxidant capacity (TAC) of the positive control showed a significant decrease in its value compared to the normal control. However, the MS groups, which were treated with black cherry juice and the mixture of the two juices, showed significant increases in their blood TAC compared to the positive control. In contrast, the black plum group showed no significant increase. However, the increases in TAC levels were less than that of the normal control group. These results indicate that the black cherry has a more potent antioxidant activity than the black plum, but the synergistic effect of the two fruits was the best in this respect. This is due to their content of phenolic compounds and anthocyanin, which play an essential role in preventing oxidation of the cell membrane lipids and hence protect the cells of the body, especially the cells of the nervous system.

Serum antibodies have both primary and pathogenic effects in MS aetiology; higher IgG1 and IgG3 levels produce more cytotoxicity in CNS cells and antibody-mediated damage (Yu et al., 2020).

Van Horssen et al. (2008) found that flavonoid-rich foods may have the potential to reduce fatigue through a variety of processes. There is currently evidence that oxidative stress may play a role in MS pathogenesis, which may be improved or reduced by flavonoids' antioxidant effects.

Furthermore, it has been claimed that flavonoids' functional qualities allow them to penetrate the blood-brain barrier, potentially resulting in better neuron signalling and neuronal function restoration (Solanki et al., 2015).

Anthocyanins derived from the bilberry (Vaccinium myrtillus L) decreased proinflammatory cytokine levels and prevented peripheral immune cell infiltration in the hippocampus, as well as myeloperoxidase activity in the cortex and hippocampus, lowering microglia (Iba-1) and astrocyte (GFAP) staining (Carvalho et al., 2017).

Intake of anthocyanins and one of their key components, cyanidin-3-O-glucoside (C3G), has been linked to a lower incidence of brain illnesses such as cerebral ischemia (Min et al., 2011; Shin et al., 2006), Alzheimer's disease (AD) (Pacheco et al., 2018; Ali et al., 2018), and Parkinson's disease (PD) (Strathearn et al., 2014; Fan et al., 2018).

One key reason for anthocyanins' neuroprotective advantages is their ability to reduce neuroinflammation and oxidative stress. These effects have been shown to protect neurons against cellular toxicities caused by factors such as ischemia/reperfusion (Min et al., 2011; Shin et al., 2006).

Table (4): Effect of black plum and black cherry juices and their mixture on blood Immunoglobulins and oxidative stress in multiple sclerosis rats.

Parameter / Groups	IgG (mg/dl)	IgM (mg/dl)	MDA (nmol/L)	TAC (μmol/L)
Normal Control	328.25±2.50 [a]	40.50±1.29 [a]	23.58±1.97 [d]	1.32±0.06 [a]
Positive Control	301.50±9.04 [c]	26.00±2.58 [c]	57.90±3.56 [a]	0.73±0.10 [c]
Black Plum	316.00±6.83 [b]	28.75±1.71 [c]	43.33±4.30 [b]	0.82±0.13 [c]
Black Cherry	314.25±4.43 [b]	41.25±1.71 [a]	34.10±3.10 [c]	0.95±0.06 [b]
Mixture of the fruits	330.50±3.70 [a]	35.50±2.08 [b]	26.78±4.75 [d]	1.07±0.06 [b]

Each value is the mean ±SD

Mean values in each column with different superscript letters are significantly different at $P \leq 0.05$.

Sujono et al. (2021) found that the extract of Jamaican cherry at dosages of 50, 100, and 200 mg/kg BW boosted the synthesis of immunoglobulin G (IgG) in a dose-dependent manner compared to the control group. According to the findings, Jamaican cherry fruits can help the immune system by acting as an immunostimulant.

Because the memory-improving effect of anthocyanins in a streptozotocin-induced rat sporadic dementia model is accompanied by a significant decrease in NO in the hippocampus and cerebral cortex, inhibition of NO production may also contribute to the neuroprotective effects of anthocyanins in AD (Gutierres et al., 2014).

Anthocyanins have been shown to boost the expression of Na+, K+-ATPase, and Ca2+-ATPase, implying that anthocyanin consumption could help restore the function of damaged neurons (Carvalho et al., 2015).

Chun et al. (2003) found that Plum extract's principal anthocyanin ingredients have been demonstrated to scavenge superoxide radicals more effectively than other flavonoids like quercetin.

3.4. Histopathological of some organs results:

3.4.1. Sciatic nerve sections:

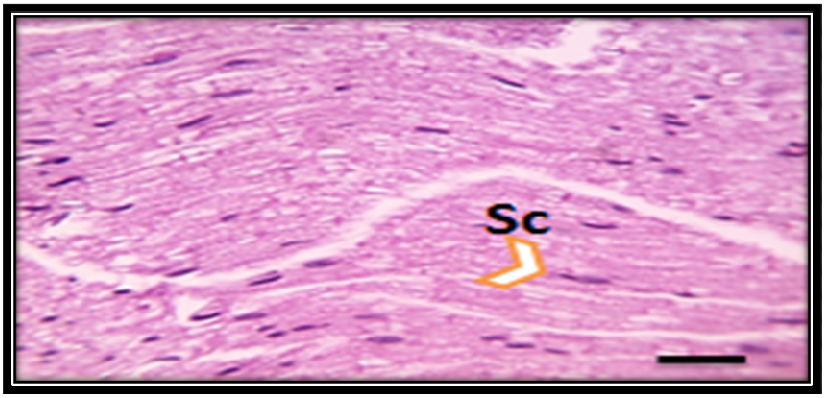

Photo (1): Sciatic nerve sections of rats from normal groups of normal Schwan cells (Sc; arrowhead), uniformly distributed myelinated fibers with regular contours, intact myelin sheath, and proportional thickness to the diameter of their axons (X: 400 bar 50).

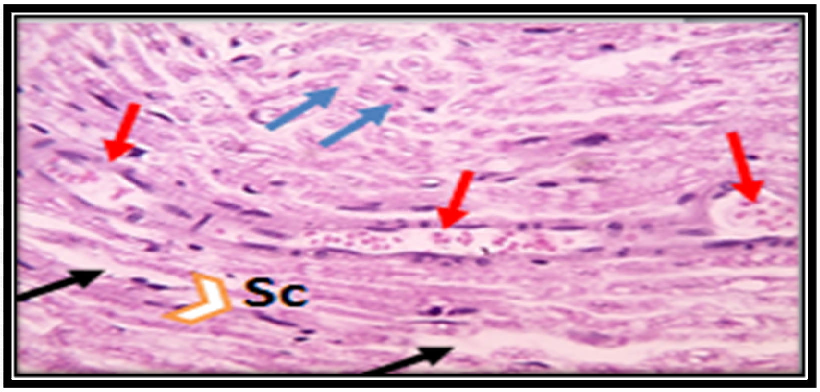

Photo (2): Sciatic nerve sections of rats from the cuprizone model showing sparsely distributed myelinated fibers with myelin sheath deformation (black arrows), axonal atrophy (blue arrows) and decreased numbers of Schwan cells (Sc; arrowhead), increased vascular proliferation (red arrows) (X: 400 bar 50).

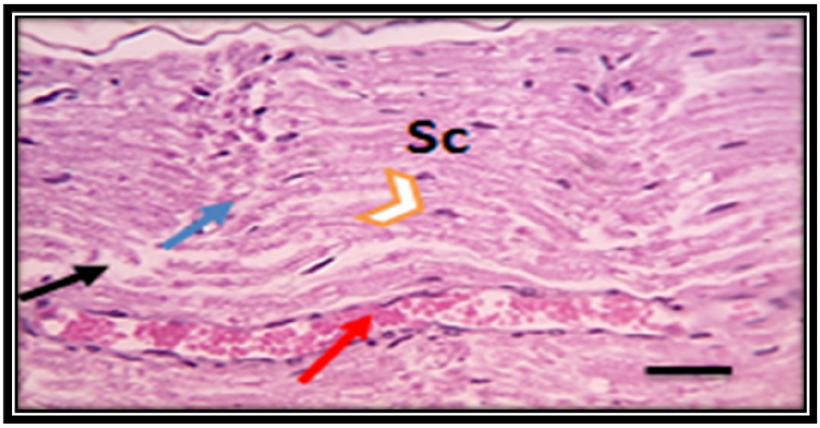

Photo (3): Sciatic nerve sections of rats from the treated group with black plum showing mildly distributed myelinated fibers (black arrows), decreased numbers of Schwan cells (Sc; arrowhead), mild axonal atrophy (blue arrows) and mildly congested blood vessels (red arrows) (X: 400 bar 50).

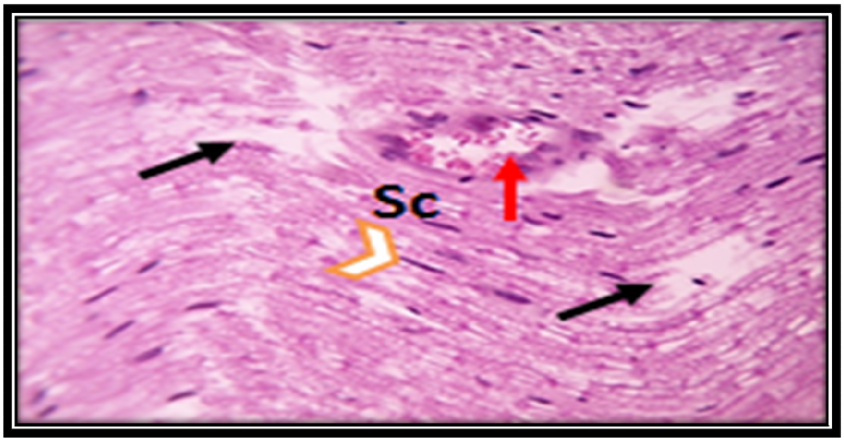

Photo (4): Sciatic nerve sections of rats from the treated group with black cherry showing mildly distributed myelinated fibers (black arrows) and mildly congested blood vessels (red arrows) with increased numbers of Schwan cells (Sc; arrowhead) (X: 400 bar 50).

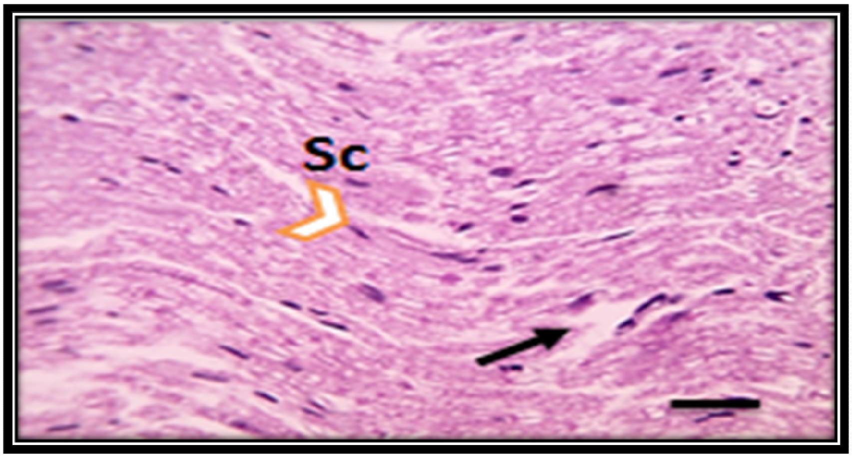

Photo (5): Sciatic nerve sections of rats from treated group with mix of black plum and black cherry (1:1) showing very mildly distributed myelinated fibers (black arrows) with much more increased numbers of Schwan cells (Sc; arrowhead) (X: 400 bar 50).

3.4.2. Optic nerve sections:

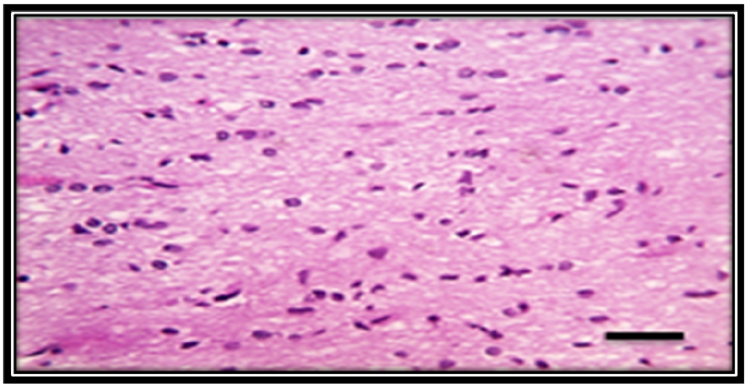

Photo (6): Optic nerve sections of rats from normal group showing normal Schwan cells (Sc; arrowhead) (X: 400 bar 50).

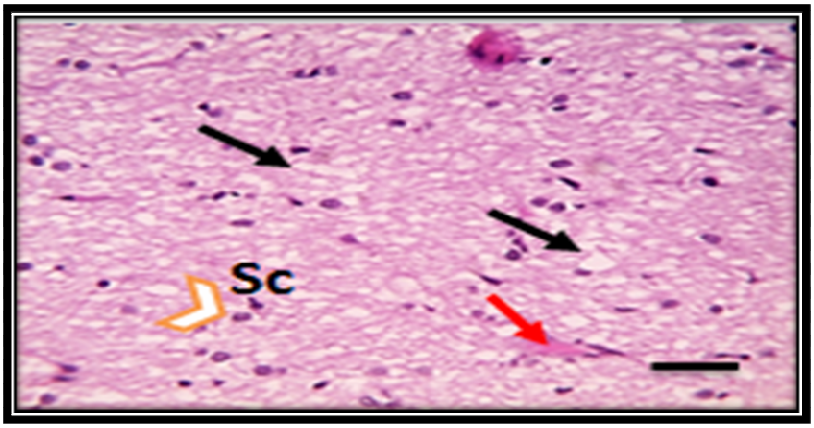

Photo (7): Optic nerve sections of rats from the cuprizone model showing marked vacuolation (black arrows), increased vascular proliferation (red arrows) and decrease numbers of Schwan cells (Sc; arrowhead) (X: 400 bar 50).

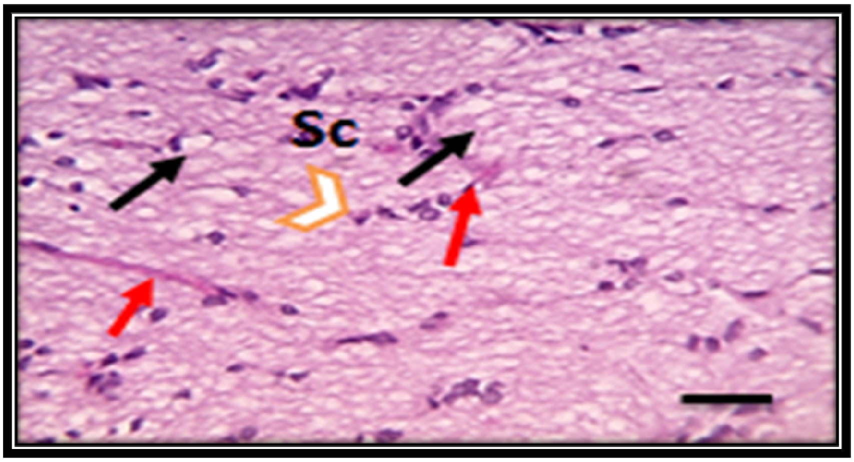

Photo (8): Optic nerve sections of rats from the treated group with black plum showing mild vacuolation (black arrows), less vascular proliferation (red arrows) with slightly increased numbers of Schwan cells (Sc; arrowhead) (X: 400 bar 50).

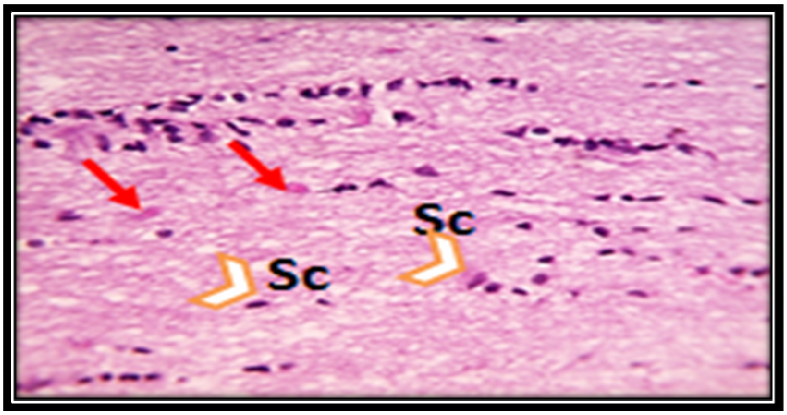

Photo (9): Optic nerve sections of rats from the treated group with black cherry showing much less vascular proliferation (red arrows) with moderately increased numbers of Schwan cells (Sc; arrowhead) (X: 400 bar 50).

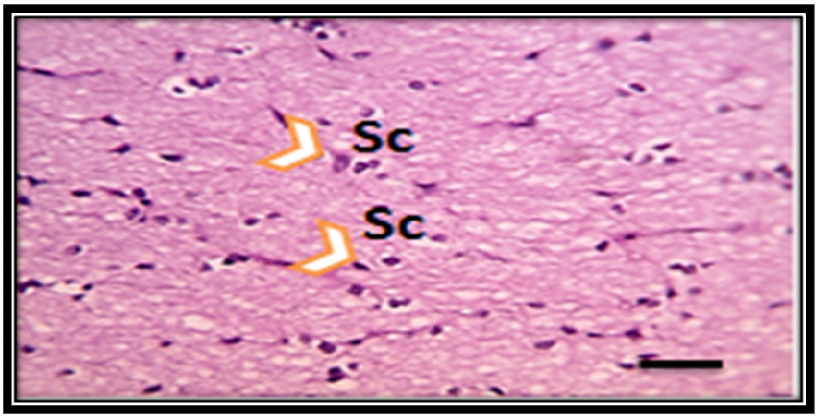

Photo (10): Optic nerve sections of rats from the treated group with mix of black plum and black cherry (1:1) showing much more increased numbers of Schwan cells (Sc; arrowhead) (X: 400 bar 50).

Groebe et al. (2009) and Lampron et al. (2015) reported that cuprizone affects the extensively myelinated corpus callosum, as well as the cerebellar nuclei, optic tracts, hippocampus, putamen, and grey matter sections of the brain. Cuprizone therapy appears to affect the cerebellum differently. The current histological findings were consistent with prior investigations that demonstrated indications of demyelination in the optic nerve (Bagchi et al., 2014; Namekata et al., 2014). Reduced myelin thickness (g-ratio) in the optic nerve has also been observed in mice fed a cuprizone diet for three weeks (Hainz et al., 2017).

4. CONCLUSION

It can be concluded that consumption of black plum and black cherry juices or their mixture decreased inflammation and oxidative stress levels in the cuprizone-induced rats, this may be due to their high content of fiber and polyphenols in addition to flavonoids, and anthocyanins. The polyphenols of the two fruits revealed antioxidant activity and high reducing power in vitro. The juices of the two fruits or their mixture showed significant improvements in the immunoglobulins in the serum of the MS rats. Also, the presence of the juice polyphenols especially anthocyanins has increased the total antioxidant capacity (TAC) in the MS rats and hence improved neural disorders such as loss of feeling or tingling, weakness or loss of muscle strength, loss of sight or double vision, memory loss, Impaired mental ability and lack of coordination indices which are important indicators in the diagnosis of Multiple sclerosis disease. Thus, our findings recommend using natural juices which are rich in polyphenols, total phenols, flavonoids, anthocyanins and ascorbic acid such as black plum and black cherry instead of sugary drinks to maintain a normal weight and prevent the complications accompanied by multiple sclerosis cases.

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استخدام عصير البرقوق الأسود والكرز الأسود في تخفيف مضاعفات التصلب المتعدد الناتجة عن الكوبريزون في الفئران

الملخص العربي:

- تهدف هذه الدراسة إلى التحقق من تأثير استخدام كل من عصير البرقوق الأسود (Prunus salicina) أوعصير الكرز الأسود(Prunus cerasus) او خليطهما في التخفيف من الآثار الجانبية الناتجة عن التصلب المتعدد (MS) في الفئران المصابة به. تم تقدير الفينولات الكلية والفلافونويد والأنثوسيانين وحمض الأسكوربيك في الفاكهة بالإضافة إلى تقدير الفعالية المضادة للأكسدة لعصير الفاكهة في المختبر.
- في التجربة البيولوجية ، تم استخدام ثلاثين من الذكور البالغين من الفئران البيضاء (وزنها ١٣٥ إلى ١٤٥ جم) ، ستة منهم كانت بمثابة مجموعة الكنترول الطبيعي (الكنترول السالب) والتي استمرت على النظام الغذائي الأساسي خلال فترة التجربة. عوملت المجموعات المتبقية بالكوبريزون بجرعة ٣ جم / كجم حمية ، تركت إحداها بمثابة (كنترول موجب) (MS control)بينما عولجت المجموعات الثلاث الأخرى يوميًا بعصائر البرقوق الأسود والكرز الأسود و خليطهم (١:١ ح / ح) بجرعة قدرها ١٥ مل / كجم باستخدام أنبوب المعدة. في نهاية التجربة ، تم ذبح الفئران وسحب دمائهم للتحليل.
- أظهرت النتائج أن جميع مؤشرات الالتهاب المذكورة CRP و COX-2 و IL-12 و TNF-α سجلت زيادة بشكل ملحوظ في المجموعة الإيجابية التي تلقت كوبريزون فقط ، بينما أظهرت المجموعات المعالجة بالبرقوق الأسود والكرز الأسود وخليطهما انخفاضًا معنويًا في مستويات عوامل الالتهاب مقارنةً بالمجموعة الموجبة.
- كما أظهرت النتائج أن مستويات IgG و IgM انخفضت بشكل ملحوظ في المجموعة الضابطة الإيجابية ، بينما أظهرت مجموعات MS المعاملة بالفاكهة أو خليطها زيادة معنوية في محتوى IgG ، بينما أدى استهلاك الكرز الأسود والمزيج إلى تحسين مستوى IgM بشكل ملحوظ مقارنة بالمجموعة الموجبة.
- أما بالنسبة للنشاط المضاد للأكسدة لمجموعات MS التي تم علاجها بعصائر الفاكهة ، وهي malondialdehyde (MDA) والقدرة الكلية المضادة للأكسدة (TAC) ، أشارت النتائج إلى أن تركيز MDA في الدم زاد بشكل ملحوظ في الكنترول الموجب ، ومن ناحية أخرى ، لوحظ أن جميع مجموعات التصلب العصبي المتعدد التي عولجت بعصائر الثمار أو خليطها أظهرت انخفاض معنوي في مستويات MDA في الدم مقارنة بالمجموعة الإيجابية. وكذلك انخفضت السعة الكلية لمضادات الأكسدة (TAC) فى المجموعة الموجبة انخفاضًا معنويًا مقارنةً بالمجموعة السليمة ، ومن ناحية أخرى أظهرت المجموعات المعالجة بعصير الكرز الأسود ومزيج العصيرين تحسنا معنويًا في مستوى TAC مقارنة بالكنترول الموجب
- الخلاصة : أدى استخدام عصائر البرقوق الأسود والكرز الأسود أو خليطهما إلى تحسن ملحوظ في كل من مستويات مؤشرات الالتهاب والإجهاد التأكسدي والجهاز المناعي في الفئران المصابة بالتصلب العصبي المتعدد الذي يُعزى على الأرجح إلى محتواها من الفينولات والفلافونويد والأنثوسيانين

الكلمات المفتاحية:

البرقوق الأسود - الكرز الأسود – الفينولات الكلية - الفلافونويد - الأنثوسيانين - MS- – DPPH - الالتهاب - TAC .