



disorders and may be by some medications.<sup>1</sup>

We can always try and save our memory or prevent it from declining by using memory enhancing foods and drugs. FDA has approved Cholinesterase inhibitors & Memantine to be the drugs of choice for Alzheimer's disease. Memantine (NMDA blocker) is considered as the drug of choice for moderate to severe stages of Alzheimer's disease.<sup>3-5</sup> Memantine works by blocking the excessive effects of glutamate that are associated with brain dysfunction, thereby preserving brain's health.<sup>5</sup>

However, nature also has various exquisite creations to solve our problem. Fortunately, we have certain foods and drugs that can help empowering our brain which in turn can prevent our memory from declining. A study shows apple contains certain flavonoids that can help enhance our memory. Apple belongs to the family rosaceae.<sup>6</sup> It contains quercetin (a flavonoid)<sup>7</sup> that has antioxidant properties.<sup>8</sup> As age-related oxidative degeneration of neurons is one of the leading cause of memory loss,<sup>8-9</sup> this antioxidant property of apple makes it a potent memory protector. Someone rightly said; an apple a day, keeps the doctor away!<sup>10</sup>

Studies reveal that consuming apples whether eating apples or drinking apple juice can be beneficial in improving brain health and may be helpful in relieving the symptoms of Alzheimer's disease.<sup>10</sup> The brain may protect by apple and apple juice consumption from oxidation-related brain damage that leads to memory loss. The brain health benefits were found when animals consumed the equivalent of 2-3 cups(8ounce) of apple juice or 2-4 whole apples per day. A clinical trial showed that drinking apple juice significantly improved mood and behavior among a group of patients diagnosed with moderate-to-severe Alzheimer's disease.<sup>11</sup>

Similarly, pear, another member of family rosaceae,<sup>12</sup> has been found to have power boosting effects on brain. Studies show pear contains copper which is considered to be healthy for our central nervous system.<sup>13</sup> Moreover, it also contains quercetin<sup>14</sup> which is already proven to have positive influence on brain's health. In addition to copper & quercetin, pears also are rich in vitamins, especially in vitamin C and vitamin K. Both of these vitamins are associated with good and strong functioning of brain.<sup>14</sup> Apple and pear also contain epicatechin (flavonoid), which has also been proved beneficial for memory.<sup>15</sup> Apples and pears are fibrous fruits. This is yet another attribute that makes them beneficial for brain functioning and

this can be helpful in the treatment of diseases like Parkinson's disease and Alzheimer.<sup>16</sup>

The aim of our study was to compare the effect of a well renowned memory enhancing drug Memantine on memory with fruits like apple (*Malus domestica*) which is speculated to be good for memory. This study also aimed to put forward the positive effects of pear (*Pyrus communis* L.) juice on memory by in vivo testing which is reported for the first time to the best of our knowledge.

### Methodology:

**In vivo Study:** This study was carried out experimentally on mice. 12 healthy adult mice of either sex were taken and divided into 4 groups, i.e. *control group*, *reference group*, *test group A* & *test group B*, each group having 3 mice. Control group was on water and normal diet, reference group was supply with memantine at a dose of 0.15mL containing 0.003mg of drug, test group A was provided with 0.15ml apple juice & test group B was given 0.15 pear juice.

Mice's behavior was evaluated using two apparatus i.e. Elevated Plus Maze for 3 days & Novel Object Recognition Chamber for 2 days. The readings were taken at time 0hrs, 6hrs & 24hrs after the administration of respective fluid for the Elevated plus Maze test, while for the Novel Object Recognition Chamber; readings were noted at time 3hrs and 6hrs after the administration of fluids.

**Sample Collection:** for phytochemical analysis, the fruit materials of *Malus domestica* and *Pyrus communis* L. were obtained from the local market of Karachi, Pakistan. First of all, fresh fruits were washed and cut into small pieces, the pericarp and mesocarp region of fresh fruit were isolated from the endocarp region (seed) and then allowed to shade dried for about 3 weeks and later made as powder by using blender and stored in air tight bottle.

**Method of extraction:** 10g of each sample powder was added to 100ml of methanol in a conical flask and plugged with cotton. After 24 hours the supernatant was collected and solvent was evaporated to make the crude extract and stored at 4°C.

### Methods for Qualitative Phytochemical Screening:

Qualitative Phytochemical analysis of methanolic extracts of *Malus domestica* and *Pyrus communis* L. was conducted for detection of alkaloids, carbohydrates, reducing sugar, glycosides and cardiac glycosides, proteins and amino acids, flavonoids,

phenolic compounds, tannins, phlobatannins, saponins, phytosterols, terpenoids, triterpenoids as well as detection of anthraquinones by the standard procedures adopted.<sup>17</sup>

### Methods for Quantitative Phytochemical Analysis:

The Phytochemicals which are present in the methanolic extracts of *Malus domestica* and *Pyrus communis* L. were evaluated for total phenols, total flavonoid, total alkaloids, total tannins and total saponins. Further all these phytochemicals were quantified by reported standard procedure.<sup>18</sup>

### Statistical analysis:

The result of *in vivo* studies is expressed using bar graphs. These bar graphs show the comparison of activities of apple juice and pear juice with the activity of standard drug Memantine on the brain function of mice. Further, results of phytochemical analysis are expressed as mean  $\pm$  standard deviation (SD).

**Ethical clearance:** All procedures done in the study were in accordance with Helsinki declaration (1964) and study was approved by the institution's ethical committee with Letter Ref. No: JUW/ ERC/158.

### Result & discussion:

Our study proves that both the supplements, i.e. apple juice & pear juice, do pose remarkably positive effects on brain's activity. The study reveals that apple juice has shown more activity among the two juices and its effect was closer to that of our standard drug i.e. memantine. We used two different apparatuses, i.e. *Elevated Plus Maze* and *Novel Object Recognition*, to evaluate and compare the activities of memantine, apple juice and pear juice on memory in mice, under same environmental and diet conditions.

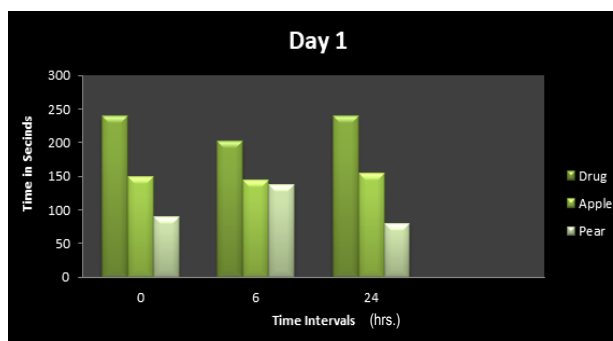
In the test with *Elevated Plus Maze*, we used a control group, a reference group and two test groups A and B, all groups were consisting of 3 mice each. Control group was not given any drug or juices, the reference group was being administered with the drug (memantine), test group A was being administered with apple juice and test group B was given pear juice. The reference group was kept on same dose for all 3 days of experiment, whereas the test groups were given same dose for first two days and on third day of experiment their doses were doubled. In this experiment, the activity of drug (Memantine) was the highest, followed by the activity of apple juice & least activity out of the three was shown by pear juice. This proportion was sustained from day 1

to day 3 (fig. 1). Individual results of each day are shown in fig. 2 (for day 1), fig. 3 (for day 2) & fig. 4 (for day 3) respectively.

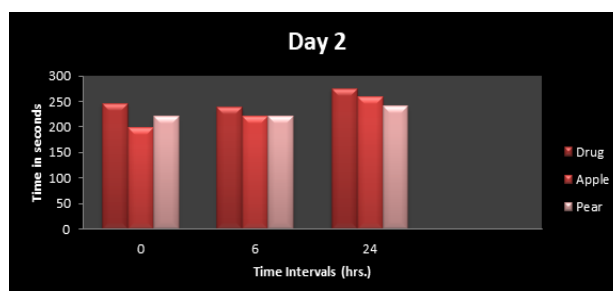
The second test, *Novel Object Recognition*, was performed on the 2<sup>nd</sup> and 3<sup>rd</sup> day of the whole study. It just confirmed and supported the results of the first test and revealed that apple juice has proven to be more effective than pear juice in enhancing the cognitive response & boosting memory in mice & its effects were closer to the effects of memantine, as shown in fig. 5 and fig. 6 respectively.

Drug	Day 1		Day 2		Day 3	
	Open arm(sec)	Close arm(sec)	Open arm(sec)	Close arm(sec)	Open arm(sec)	Close arm(sec)
Apple	145	155	40	260	68	239
Pear	220	80	60	240	65	235

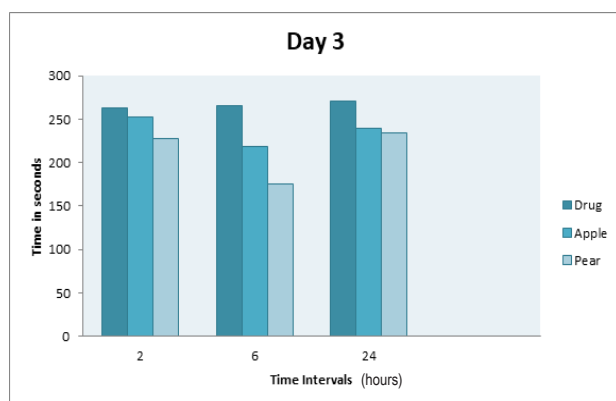
**Fig. 1:** Observed readings with *Elevated plus Maze* test



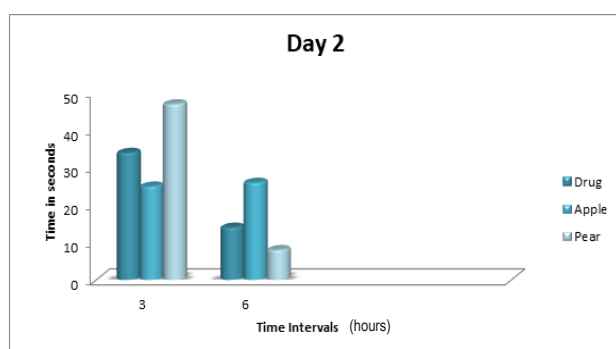
**Fig. 2:** Compare the activity of drug (memantine) with apple and pear juices at day 1. Activity was checked at 0 hour, 6 hours and 24 hours after given a single dose of 0.15mL containing 0.003mg of drug and 0.15mL of apple and pear juices.



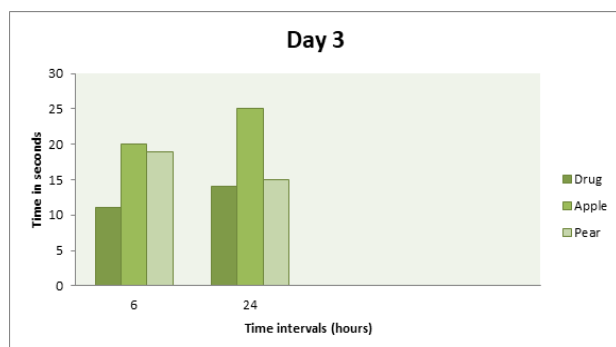
**Fig. 3:** Compare the activity of drug with apple and pear juices at day 2. Activity was checked at 0 hour, 6 hours and 24 hours after given a single dose of 0.15mL containing 0.003mg of drug and 0.15mL of apple and pear juices.



**Fig. 4:** Compare the activity of drug with apple and pear juices at day 3. Activity was checked at 2 hours, 6 hours and 24 hours after given a doubled dose.



**Fig. 5:** Compare the activity of drug with apple and pear juices at day 2 using novel object recognition after giving a dose of 0.15mL containing 0.003mg of drug and 0.15mL of apple and pear juices.



**Fig. 6:** Compare the activity of drug with apple and pear juices at day 3 using novel object recognition after giving a dose of 0.15mL containing 0.003mg of drug and 0.15mL of apple and pear juices.

Increasing evidence has shown that health-promoting properties of many beneficial fruits are mainly due to their phytochemical constituents; especially phenolic compounds. According to the Tables 1 and 2; confirm

the existence of different phytochemicals present in both fruits categories as with peel, without peel and only peels by quantitative and qualitative methods, which includes all of these; alkaloids, carbohydrates, reducing sugar, glycosides, cardiac glycosides, proteins and amino acids, flavonoids, phenolic compounds, tannins, Phlobatannins, Saponins etc.

#### Qualitative phytochemical analysis:

The observed results of phytochemical Analysis were signifying positive results in alkaloids, carbohydrates, glycosides, protein, flavonoids and phenolic compounds etc. as shown in Table 1 for both fruits (Apple & Pear). Quercetin is flavonoid and epicatechins are phenolic compounds present in apple as well as in pear. The maximum amounts of these two beneficial phytochemicals are present in fruits with peels as compare with two others tested samples.

Fruits which are rich in polyphenols have been found to be helpful to brain function. Phenolic compounds show high concentration in most types of the studied. Increasing evidence has shown that health-promoting properties of fruits are mainly due to their phytochemical constituents; especially phenolic compounds.<sup>19</sup> The phenolic compounds are one of the major and most abundant groups of plant metabolites. Numerous, phyto-active compounds like phenolic compounds in plants consist of a moderately large class of secondary metabolites with varies potential bioactivities<sup>20-21</sup>, such as antioxidant, antibacterial, and anti-inflammatory.<sup>22-23</sup>

Natural antioxidant mainly comes from plants in the form of phenolic compounds such as flavonoid, phenolic acids, etc.<sup>24</sup> Flavonoids are hydroxylated phenolic substances identified to be synthesized by plants in reaction to antimicrobial matter against pathogen microorganisms in *in-vitro* studies. They also are effective antioxidants and demonstrate strong anticancer actions.<sup>24</sup>

Diets wealthy in plant-derived polyphenols have been exposed to decrease oxidative stress and inflammation, thus lowering the danger of non-communicable diseases based on a chronic inflammatory state (e.g., cancer, neurodegenerative diseases, cardiovascular diseases, obesity and diabetes). Daily serving of apples and pears in older people lacking a Mediterranean-style diet is positively connected with a reduced hazard of colorectal cancer.<sup>25</sup> The antioxidant mechanisms described in many studies have important implications for a protective

effect of apple and pear on not only cancer but also on cardiovascular disease, asthma, Alzheimer's disease, and potentially diabetes. Though, there are provocative data suggesting that mechanisms beyond antioxidant effects are significant, including suppression of neurotoxic mediators in Alzheimer's disease.<sup>26</sup>

Rising indication suggests that Alzheimer's disease oxidative injury caused by the beta-amyloid peptide in the pathogenesis may be hydrogen peroxide mediated. Numerous polyphenols, the chief abundant dietary antioxidants, have stronger neuroprotection in human being.<sup>27</sup>

**Table 1: Qualitative Phytochemical Contents of Apple (*Malus domestica*) and Pear (*Pyrus communis*L)**

S. No.	Name of test	Apple			Pear		
		With peels	Without peels	Only peels	With peels	Without peels	Only peels
1	<b>Detection of alkaloids</b> Mayer's test	+	+	+	+	+	+
2	<b>Detection of carbohydrates</b> Bardfoed's test	+	+	+	+	+	+
3	<b>Detection of reducing sugar</b> Fehling's test	-	-	-	-	-	-
4	<b>Detection of Glycosides</b> Conc. H <sub>2</sub> SO <sub>4</sub> test	+	+	+	+	+	+
5	<b>Detection of cardiac glycosides</b> Keller – Killani test	-	-	-	-	-	-
6	<b>Detection of protein and amino acids</b>						
	a. Biuret test (amino acid) b. Xanthoproteic test (protein)	- +	- +	- +	- +	- +	- +
7	<b>Detection of flavonoids</b>						
	a. Alkaline reagent test	+	+	+	+	+	+
	b. Lead Acetate test c. Conc. H <sub>2</sub> SO <sub>4</sub> test	+ +	+ +	+ +	+ +	+ +	+ +
8	<b>Detection of phenolic compounds</b> Lead Acetate test	+	+	+	+	-	+
9	<b>Detection of Tannins</b>						
	a. Gelatin test b. Braymer's Test	+ -	+ -	- -	+ -	+ -	- -
10	<b>Detection of Phlobatannins</b> HCl test	-	-	-	-	-	-
11	<b>Detection of saponins</b> Frothing Test	+	-	-	+	-	+
12	<b>Detection of Phytosterols</b> Salkowski's test	-	+	+	-	+	+
13	<b>Detection of Terpenoids</b> General test	-	-	-	-	-	-
14	<b>Detection of Triterpenids</b> Salkowski's test	+	+	+	-	+	-
15	<b>Detection of Anthraquinones</b> Borntrager's test	-	-	-	-	-	-

\*Note: (+) = positive result while (-) = negative result.

### Quantitative results of phytochemical analysis:

The results showed that the maximum amounts of alkaloids were present in the apple and pear with peels 12.96% & 23.13% as compared to without peels 5.50% & 15.16% and only peels 7.46% & 18.93%.

Maximum results shown significantly increment in fruits with peels (table 2), so it is recommended that fruits with peels contains more useful alkaloids which are helpful and responsible to treat Alzheimer's disease and also helpful in memory enhancement.<sup>28</sup> Analysis show that the highest percentage of

tannins was observed in the peeled apple and pear fruit 0.147% & 0.011% respectively as compared to the fruits without peels and only peels. Tannins are biological molecules with many pharmacological properties, including, especially neuro-protection. They improve the symptoms of Alzheimer's disease (AD), Parkinson's disease (PD) by retarding their pathogenesis through the attenuated production of varied cytotoxic factors. As just in case of AD, tannins hinder the buildup of A $\beta$  peptides and thereby offer a defensive role against the disease's pathogenesis and progression.<sup>29</sup> The results of the study revealed that both apples and pears with peels contained maximum proportion of saponins 3.86% & 2.1% respectively, while the fruits without peels contained the lesser percentage. Apple contains 1231.601 % phenols in with peeled fruit as compared to the fruit without peel and only peels. Also in the pear, the maximum amount was observed in the fruit with peels 3263.20%. There are a number of epidemiological studies that suggest that plant-based foods or supplements rich in polyphenols can delay the onset and progression of AD, PD, and related neurodegenerative diseases.<sup>30-31</sup> The neuro-protective effects of dietary polyphenols include a number of effects on the brain, including the potential to protect neurons from neurotoxin-induced injury, the ability to suppress neuro-inflammation, and the potential to increase memory, learning, and support for memory. Cognitive function financially. Apple juice has a significant concentration of

natural low molecular weight phenols (including chlorogenic acid, flavonoids and flavanols) and pro-cyanidins which, due to their antioxidant effects, can protect against age-related diseases that help decrease the probability of cancer and Alzheimer's disease. Research suggests that apple juice increases acetylcholine in the brain, potentially leading to better memory. The analysis show that the highest percentage of flavonoids was registered in the peeled apple and pear fruits i.e. 35.92% and 33.57% respectively as compared to the fruits without peels and only the peels. Evidence has begun to emerge that these low relative molecular mass, non-nutrient components could also be liable for the beneficial effects of flavonoid-rich foods in vivo, through their ability to directly or indirectly interact with the brain's innate architecture for memory<sup>32-33</sup>. Apples are well-off in quercetin, a type of phytochemicals called flavonoids. Rising evidence suggests that the oxidative injuries caused by amyloid beta peptide in the pathogenesis of Alzheimer's disease possibly mediated by hydrogen peroxide. Many polyphenols, the most common antioxidants in foods, have more neuro-protection against hydrogen peroxide than antioxidant vitamins. Fruit and vegetable juices can play an important role in delaying the onset of Alzheimer's disease, particularly in those who are at high risk for the disease<sup>34-35</sup>. These outcomes could guide to a new approach to research in the prevention of Alzheimer's disease.

**Table 2: Quantitative analysis of phytochemicals**

Name of Test	Apple			Pear		
	With peels	Without peels	Only peels	With peels	Without peels	Only peels
Total Alkaloids %	12.96 ± 2.15	5.5 ± 0.65	7.46 ± 0.83	23.13 ± 1.20	15.16 ± 0.76	18.93 ± 0.55
Total Tannins %	0.14±0.009	0.01±0.004	0.01±0.001	0.0117 ±0.0008	0.0012 ± 0.0002	0.0042 ±0.0008
Total Saponins %	3.86±0.32	1.8±0.26	2.06±0.70	2.1±0.36	1.7±0.62	1.9±0.51
Total Phenols %	1231.60 ± 167.81	227.55 ± 27.02	1018.97 ± 92.40	3263.205 ± 241.15	205.75 ± 15.60	1111.02 ± 229.84
Total Flavonoids %	35.92 ± 3.11	22.15 ± 1.69	30.35 ± 1.09	33.57 ± 2.23	32.24 ± 1.55	32.97 ± 1.88



**Conclusion:**

Memantine is an FDA-approved drug for Alzheimer's disease and produces marvelous effects on memory and brain's activity. The effects of apple juice on mice's cognitive behavior were closest to the effects of memantine as compared to pear juice. It is concluded that the presence of several bioactive compounds in apple as well as in pear could be responsible for memory enhancing effects. This may further promote a confidence for the progress for many more innovative drugs. Further, phytochemical analysis shown significantly increment in fruits with peels, so it is recommended that fruits with peels contains more beneficial phytochemicals which are helpful and responsible to treat Alzheimer's disease and also helpful in memory boosting.

**Recommendation:** Apples and Pears could consider as remarkable natural source of active compounds for drug development and future pharmacological studies.

**Source of fund (if any):** No funding has been provided for this working.

**Conflict of interest:** The authors declare that the investigation was accompanied in the absence of any commercial or financial associations that could be interpreted as a potential conflict of interest.

**Author's contribution:**

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Study design: Somia Gul and Rabia Badar

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Editing and approval of final draft: Somia Gul

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