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Systematic Review

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Effect of Grape and its Derivatives on Cognitive Function: A Systematic Review of Clinical Trials

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Abstract

Background: According to the world health organization (WHO), in 2019, around 50 million people suffer from dementia, worldwide; and approximately 60% live in low- and middle-income countries. Dementia has physical, psychological, social, and economic effects on dementia sufferers, their caregivers, families, and the community.

Objectives: This systematic review investigated the effect of short-term and long-term interventions with grapes and their derivatives on different cognitive functions, such as executive function, memory, attention and language in all people.

Methods: Pubmed, Scopus, and Proquest were searched until June 12, 2020 for English studies. Clinical trials in which grapes and its derivatives were considered as an intervention and changes of cognition and its components as an outcome, were selected. Two independent individuals assessed the quality of the articles according to Jadad checklist and extracted the information of the articles with inclusion criteria based on a specific table. The differences were resolved with the discussion and opinion of a third person.

Results: Nine Studies (211 individuals) were included in the content analysis, of which 3 studies had short-term intervention and 6 studies had long-term intervention with grape juice, freeze-dried grape powder, and a syrup made from grapes (Enoant Syrup). It can be said that the consumption of grapes and its derivatives improved various cognitive components (such as attention, executive function, immediate spatial memory, learning, and driving skill) between groups.

Conclusion: In general, long-term intervention with grapes and their derivatives has led to the improvement of some cognitive functions, but its short-term intervention is not very effective and only 2 studies showed improvement in attention speed. However, the included studies were highly heterogeneous and more research is needed using similar cognitive assessment tools.

Keywords: Vitis, Grape, Cognition, Cognitive Function, Memory

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Introduction

Cognition is the ability of an individual to process information through sense and experience in trying to learn knowledge and decision making [1]. It has components, including memory, language, orientation, judgment, interpersonal communication, actions, and problem solving. Mild cognitive impairment (MCI) is a degree of cognitive impairment that does not require a diagnosis of dementia and maintains the basic activities of daily life, which can be a warning sign for Alzheimer's disease [2]. According to a meta-analysis of 7 studies in 2019, the incidence of MCI per 1000 people per year was 22.5 for the ages 75-79, 40.9 (7.7-97.5) for the ages 80-84, and 60.1 (6.7-159.0) for those aged over 85 years. [3] According to the world health organization (WHO), in 2019, around 50 million people suffered from dementia, worldwide; and approximately 60% of them lived in low- and middle-income countries. There are also nearly 10 million new cases every year. The number of people with dementia is predicted to reach 82 million in

2030 and 152 million in 2050. Dementia has physical, psychological, social, and economic effects on patients and their caregivers, families, and the community [4]. Risk factors include neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Louis body dementia, etc.), physiological (normal-pressure hydrocephalus) and metabolic disorders (vitamin B12 and folic acid deficiency, endocrinopathy such as hypothyroidism, chronic metabolic disorders, such as uremia), tumor, trauma, infection, cardiovascular disease, medications, toxins, APOE4 allele status, cerebrovascular events, and chronic high cortisol levels [2]. On the other hand, the brain is prone to oxidative stress with high oxygen consumption and high fat content. Therefore, oxidative stress damage to the brain is a strong stimulus which negatively affects the normal functioning of the central nervous system [5].

Polyphenols are compounds with potentially diverse biological properties and can be useful against oxidative stress, inflammation, the negative effects of aging, and etc. [6]. The dietary polyphenols protect neurons from damage caused by neurotoxins, suppress neuronal inflammation, and improve memory, learning, and cognitive function [7]. The most important active compounds in grapes are phenolic compounds [8], the most prominent of which are phenolic acid, flavanol, flavonol, anthocyanin, and acetylbene. These compounds have antioxidant, antibacterial, anti-inflammatory, anti-diabetic properties and also have protective effects on the skin, liver, heart, and the brain [9].

Some studies have shown the improving effects of grapes and their derivatives on cognition [10-12] and others have not listed any effect [13, 14]. We are not aware of a systematic review trying to separate the long and short-term effects of intervention with grapes and their derivatives on cognition; therefore, the present study was conducted.

Method

Data sources and search strategy

This systematic review is reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [15]. The search strategy to find related studies in English language was applied in Pubmed, Scopus, and Proquest databases (to find thesis) up to June 12, 2020. The keywords titled "MeSH" and other related phrases selected in the search strategy are as follows:

(((Vitis*[MeSH] OR grape[tiab] OR raisin[tiab] OR currant[tiab]))) AND (Cognition[MeSH] OR cognitive[tiab] OR "neurobehavioural manifestations"[tiab] OR volition[tiab] OR delirium[tiab] OR dementia[tiab] OR amnestic[tiab] OR "response interference"[tiab] OR learning[MeSH] OR Memory[MeSH] OR "item recall"[tiab] OR remembering[tiab] OR reminiscence[tiab] OR amnesia[tiab] OR "neuropsychological status"[tiab] OR demention[tiab] OR perception[tiab] OR perceptual[tiab] OR "size detection"[tiab] OR "size discrimination"[tiab] OR "size perception"[tiab] OR attention[tiab] OR motivation[tiab] OR "motor control"[tiab] OR "psychomotor skill"[tiab] OR responsiveness[tiab] OR executive[tiab] OR Planning[tiab] OR calculation[tiab] OR language[tiab] OR naming[tiab] OR writing[tiab] OR reading[tiab] OR praxia[tiab] OR praxis[tiab] OR orientation[tiab] OR judgment[tiab] OR evaluation[tiab] OR reasoning[tiab] OR computation[tiab] OR "problem solving"[tiab] OR "decision making"[tiab] OR comprehension[tiab] OR Gnosis[tiab] OR "Visuospatial Skills"[tiab])

To manage data sources, eliminate duplicates, and facilitate the systematic review process, the studies were transferred from databases to Endnote (version X9) software.

Inclusion criteria

The studies included in this systematic review should have the following characteristics:

1) Studies with randomized controlled clinical trial design, 2) Studies which used grapes or one of its derivatives containing a set of its polyphenols and micronutrients and without change due to cooking and fermentation (and not just a specific type of polyphenols) for intervention and another source of polyphenols has not been used as an intervention (such as grapes + blueberries), 3) published in English language.

Study selection, quality control, and data extraction

After screening titles and/or abstracts, full-texts of the studies were carefully checked. The quality of each study was confirmed through two independent individuals by using Jadad quality control checklist [16], and the cases that do not agree on them were consulted, and the final result was recorded.

Data extraction

Two independent reviewers extracted the relevant data according to a specific table, through which general information (author's surname, year of publication, and type of study design), characteristics of the study participants (number, health status, age, sex, intervention, and placebo), purpose of the study (evaluation of the effect of intervention on cognition by method or questionnaire), and the results (often significant results with P <0.05 between the intervention and control groups) were collected.

Results

Search results

Until June 12, 2020, 2237 studies were identified from three databases. After eliminating duplicates, 1884 publications were remained that were screened, 1775 articles did not meet the inclusion criteria in terms of title and abstract. Of the remaining 9 cases, all [10-14, 17-19] were used for qualitative analysis. The flow chart of the study is shown in **Figure 1**.

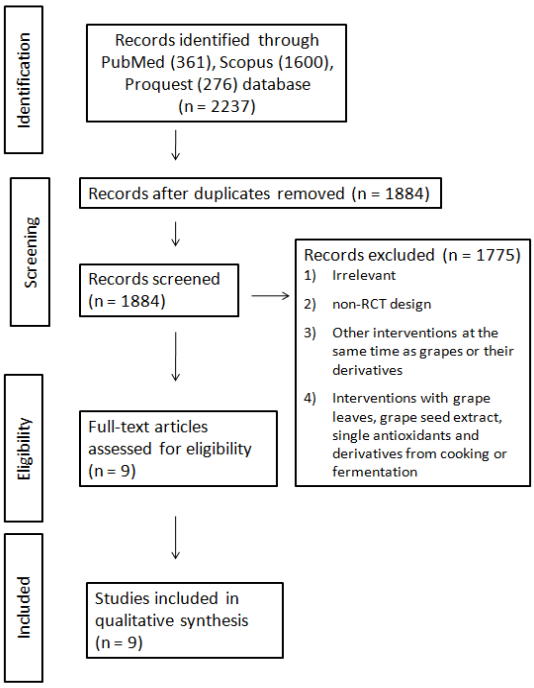

Figure 1: Identification process for eligible studies

In the remaining studies, the effects of grape juice (7 studies; 4 long-term studies [10-12, 19], and 3 short-term studies [13, 18, 20]), freeze-dried grape powder (1 case) [14], Enoant Syrup (1 study) [17] on different areas of cognition (memory, attention, response speed, executive function, visual-spatial performance, recall, psychomotor skills, language, and estimated verbal IQ by different methods), and driving skill (as a multiple skill from different cognitive domains by designed virtual driving) were evaluated.

Study characteristics

The 9 studies (211 individuals) used in the qualitative analysis are summarized in **Table 1**. These studies were conducted from 2008 to 2020 and had a sample size of 10 to 43 people. Participants ranged from healthy to elderly people with mild cognitive decline.

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Short-term intervention studies

In a study by Haskell et al. [18] in 2017, in healthy individuals, purple grape juice significantly reduced the reaction time for

attention in the intervention group compared to the placebo group. Other cognitive items did not change significantly. In another study by the same person [20] in 2013, the Concord grape juice increased the speed of attention in the intervention group compared to the placebo group, but this intervention had no effect on memory. On the other hand, in a study by Hendrickson [13] in young smokers, Concord grape juice showed no change in implicit memory in the intervention group compared to the placebo group.

Long-term intervention studies

The study by Helmer et al. [19] on veterans with Gulf War illness had a significant increase in executive function (using RCAT) after adjusting baseline differences in the intervention group compared to the placebo group at the end of the study. In the study by Lamport et al. in 2016 [10], immediate spatial memory was significantly increased in the intervention group compared to the placebo group, but no change was observed in other cognitive items, including executive function (examined using RVIP). In this study, driving performance as a multi-skill of cognitive domains had a significant improvement in the intervention group compared to placebo. In the Krikorian study in 2010 [12], learning performance was significantly improved in the intervention group (Concord grape juice) compared to the placebo group. In another study by the same person in 2012 [11], in the placebo group, interfering errors in memory was increased compared to the intervention group, indicating the protective effect of grape juice in reducing memory errors. In Brunner's study in 2013 [17], no significant change was observed between the two groups, but in the intervention group, compared to the first level, there was a significant increase in attention. In a study by Lee et al. in 2016 [14], with the intervention of grape powder, no change was observed between the intervention and placebo groups in terms of psychological tests, but a negative correlation was observed between the combined measure of two brain regions metabolism (rSPL and liLAT) with improved performance in two areas of cognition (attention / working memory) in the intervention group ($r = -0.69$, $P = 0.04$).

Discussion

In general, this systematic review was done to study the effect of grapes and their derivatives on cognitive function. The consumption of grapes and its derivatives improved a number of cognitive components (such as attention, executive function, and immediate spatial memory, learning, and driving skill) in the intervention groups compared to control groups. Modulation of neuro inflammation [21], improvement of cerebrovascular function [22], change in intestinal microbiota [23], glucoregulation [24], and increase in spinal density and neurogenesis especially in hippocampus [25] are potential direct and indirect mechanisms in improving cognition by polyphenols.

The results of three studies with short-term intervention (same-day effect study) [13, 18, 20] of grape juice in healthy individuals in the young age group, showed the ineffectiveness of this intervention on several parameters. Only cognitive case in the intervention group was significantly different from the placebo and the attention rate was in 2 studies. This ineffectiveness could be due to the very short duration of intervention versus long-term interventions (between 12 to 24 weeks for studies with significant results between the two groups studied in this study) [10-12, 19] and also the age of the participants (young participants).

Table 1: Characteristics of eligible studies.

Reference / year	Population / study characteristics	Intervention	Placebo	Purpose of the study	Main and often significant results	Jadad Score(?/5)
Krikorian 2009	12 old adult with memory impairment (not dementia) (8 males and 4 females) mean age of 78.2 years(y) RCT / double-blind / placebo-controlled / long term	6-9ml / kgbw pure Concord grape juice(CGJ) in equal divided doses with 3 meals of breakfast, lunch and dinner per day for 12 weeks(W)	6-9ml / kg placebo drink without natural polyphenols but matched in appearance, energy and carbohydrate composition per day for 12 weeks	Evaluation of the effect of pure Concord grape juice on cognition (2 areas): 1) Verbal learning and recall: CVLT 2) Non-verbal memory: S-PAL	Increased verbal learning in CVLT in the intervention group compared to placebo (P = 0.04)	2
Krikorian 2012	21 old adults with mild cognitive impairment (11 males and 10 females) with a mean age of 76.9 y RCT / double-blind / placebo-controlled / long term	6.3-7.8 ml / kgbw pure CGJ in equal divided doses with 3 meals of breakfast, lunch and dinner per day for 16 W	6.3-7.8 ml / kgbw placebo drink without natural polyphenols but matched in appearance, energy and sugar profile for 16 W	Evaluation of the effect of pure CGJ on memory function using CVLT	No effect of placebo intervention on learning in CVLT Increase of memory interference errors in placebo group compared to intervention (P = 0.04)	2

Reference / year	Population / study characteristics	Intervention	Placebo	Purpose of the study	Main and often significant results	Jadad Score(?/5)
Lamport 2016	19 healthy working mothers (40-50 years) (total) 10 of 19 cases to measure driving performance RCT / double-blind / placebo-controlled / crossover (with 4 W wash out period) / long term	12 ounces or 355 ml of pure CGJ per day for 12 W	12 ounces or 355 ml placebo drink without polyphenols but matched in appearance, energy and content carbohydrates per day for 12 W	Evaluation of the effect of pure CGJ on 1) cognitive function and 2) driving, respectively, using: 1) Cognitive function: - Immediate recall(verbal memory): VVLT - Immediate recall (non-verbal spatial memory): VSLT - Executive function: RVIP / TOH - Psychomotor skills: Grooved Pegboard - Delayed recall: VVLT / VSLT 2) Driving: Virtual driving of chasing cars and keeping track	Increased immediate spatial memory in the intervention group compared to placebo (P <0.05) Improvement in driving performance in the intervention group compared to placebo (P = 0.05) Significant reduction in TOH completion time with intervention compared to placebo in phase 1, taking into account the effect of the study phase (P <0.01) Significant improvement of immediate recall in placebo group, considering the effect of study phase (this effect is seen when placebo is used in phase 2 compared to phase 1, which indicates the persistence of positive effects of CGJ)	5
Helmer 2020	31 veterans with Gulf War illness (with a range of respiratory, gastrointestinal and neurological symptoms) (42-65 y) (81% male) RCT / double-blind / placebo- controlled / long term	16 ounces of pure CGJ per day for 24 W	16 ounces of placebo drink without natural polyphenols but matched in appearance, energy and glucose profile per day for 24 W	Evaluation of the effect of pure CGJ on cognition (5 areas): - Attention and speed of response: WAIS-IV / CPT-3 / Trail A - Memory: CVLT-2 / BVMT-R - Visual-spatial function: WAIS-IV - Executive function: Stroop color & word test / RCAT / Trail B - A result of the 4 mentioned areas with equal weights in:GCFS	Increased executive function in RCAT in the intervention group compared to placebo after matching initial differences (P = 0.04)	5

Reference / year	Population / study characteristics	Intervention	Placebo	Purpose of the study	Main and often significant results	Jadad Score(?/5)
Lee 2016	10 individuals with mild cognitive decline (5 males and 5 females) with a mean age of 72.2 y RCT / double-blind / placebo-controlled / pilot / long term	72 g freeze-dried grape powder mixed with 16 ounces of water equivalent to 3 units of fresh grape daily for 24 W	72 g matching placebo formulation in appearance, energy and fructose and glucose content per day 24 W	Evaluation of the effect of grape powder on cognitive function using PET-scan with sVOI and SPM and also a set of neuropsychological tests including: - General assessment: ADAS-cog / MMSE - Memory: VLT / Benton visual retention test / Ray-osterreith complex figure test delayed - Language: Boston naming test / Letter fluency FAC/ CFT - Executive function: Stroop interference / Trail B / WCST-64 - Information processing speed: Trail A / WAIS-2 symbol speed / WAIS-3 digital symbol - Spatial visual: Ray-osterreith complex figure test /WAISIII Block Design / WAIS-III Symbol search total - Attention and executive memory: WAIS-III Letter- Number Sequencing / WAIS-III Digital Span - Estimated verbal IQ: WATR - Memory reported by the person: Memory Functioning Questionnaire	No statistically significant difference between the two groups related to neuropsychological tests Correlation: combined measure of rSPL and liLAT with improved neuropsychological function in attention / working memory WAIS-3 digital span in the intervention group (P = 0.04 and r = -0.69)	4

Reference / year	Population / study characteristics	Intervention	Placebo	Purpose of the study	Main and often significant results	Jadad Score(?/5)
Brunner 2013	43 students (23 intervention cases (7 men and 17 women) and 20 placebo cases) in conditions of increased intellectual load RCT / long term	35 ml Enoant syrup (containing all polyphenols and grape micronutrients) daily for 20 days after breakfast	Not stated	Evaluation of the effect of Enoant syrup on cognition and personality domain using: - MMPI - Auditory arbitrary memory: Luria'smethod "10 words learning / Jacobson'smethod - Attention: Landolt'sophthalmologic rings -Attention quality, speed of sensorimotor reaction and thinking operation: Choice "and" Decision-making "tests (by PFS software)	No statistically significant difference between the two groups related to psychological tests Improvement of attention parameters in the intervention group compared to the initial level Improvement in all 13 baseline MMPI scores in 7 boys in the intervention group compared to baseline Improvement in all 13 baseline MMPI scores in 17 girls except the "Lie" score in the intervention group compared to baseline	0
Haskell 2017	20 healthy young adults with a mean age of 21.05 y (7 males and 13 females) RCT / double-blind / placebo-controlled / crossover(with 6-7 days wash out period) / short term	230 ml purple grape juice as a single dose	230 ml placebo matched in appearance, energy and sugar	Evaluation of the effect of purple grape juice after 20 minutes of absorption on cognition using software COMPASS (computerized mental performance assessment system)	Reduced reaction time for attention action (P = 0.047) in the intervention group compared to the placebo group	5

Reference / year	Population / study characteristics	Intervention	Placebo	Purpose of the study	Main and often significant results	Jadad Score(?/5)
Hendrichson 2008	35 smokers with a mean age of 26 y (17 men and 18 women) RCT / double-blind / placebo-controlled / crossover (with 1 W wash out period) / short term	10 ml/ kgbw pure CGJ with the same custom lunch as a single dose	10 ml / kgbw placebo matched in appearance, energy and sugar with the same custom lunch	Evaluation of the effect of CGJ on implicit memory using WFC	No change in implicit memory (The accuracy of WFC test before the intervention was unexpectedly correct and was higher in the intervention group before the intervention than in the placebo group (P <0.05))	2
Haskell 2013	20 healthy young adults RCT / double-blind / placebo-controlled / crossover / short-term	200 ml CGJ as a single dose	200 ml Placebo matched in taste and sugar	Evaluation of the effect of CGJ after 20 minutes of absorption on cognition with computerized indicators	Increased attention speed in the intervention group compared to placebo (P <0.05) No change in memory between the two groups	-

CVLT: California verbal learning test, S-PAL: Spatial paired associate learning test, fMRI: functional magnetic resonance imaging, VVLT: visual verbal learning test, VSLT: visual spatial learning test, RVIP: rapid visual information processing, TOH: tower of Hanoi, WAIS: Wechsler Adult Intelligence Scale, CPT-3: Conner's Continuous Performance Test-3, Trail A or B: Trail Making Test A or B, BVMT-R: Brief Visuospatial Memory Test-Revised, RCAT: Halstead Category Test—Russell Revised Version, GCFS: Global Cognitive Functioning Score, sVOI: standardized volumes of interest, SPM: statistical parametric mapping, ADAS-Cog: Alzheimer's Disease Assessment scale, cognitive subscale, MMSE: Mini-mental Status Exam, VLT: Hopkins Verbal Learning Test – Revised, CFT: Category Fluency Test, WCST-64: Wisconsin Card Sorting Test -64, WATR: Wechsler Test of Adult Reading, LiLAT: Left Inferior Lateral Anterior Temporal Cortex, RsPL: Right Superior Parietal Cortex, MMPI: Minnessota Multiphasic Personality Inventory, COMPASS: Computerized Mental Performance Assessment System, WFC: word fragment completion

In studies with long-term intervention, it was observed that 2 studies showed an improved memory or reduced memory errors [10, 11], 1 study improved executive function [19], 1 study improved learning performance [12], and 1 study improved driving skill [10]. Also in a study by Lee et al., an inverse correlation of rSPL and liLAT combined measurements with performance improvement in two areas (attention/working memory) was observed in the intervention group. The fact that in all these studies not all parameters of cognition changed or a single parameter did not change in the studied cases, could be due to the use of different psychological methods with different sensitivity and specificity, small sample size, non-random clustering in cases with large baseline differences, the effect of practice in crossoverstudies (better response in the second phase than the first phase), and inadequate wash-out periods (insufficient even up to 4 weeks).

In two of the studies, the activity of brain regions was also examined. Both studies showed that the activity of the right upper parietal cortex in the grape intervention group was changed compared to the placebo group; the first study used PET-scan and showed a significant increase (P = 0.03) [14] and the second study used fMRI and showed a marginal increase (P = 0.07) [11]. Therefore, it can be expected that improving the activity in this area with this intervention can lead to improvement in working memory and speed of attention, since this part plays a role in working memory and attention [26-30] and this result is a further confirmation of the results obtained from the mentioned effect of grapes on these cognitive domains.

The appropriate quality of articles in qualitative analysis and conclusions based on the duration of the intervention was the strength of this study. The low number of studies with the same psychological assessment tools and short-term clearance periods in cross-over studies (2 weeks) (the effect of the intervention was not eliminated in the group that intervened first after the placebo group) were the limitations of the study.

Conclusion

In general, this study showed that the long-term intervention with grapes and their derivatives might lead to an improvement in memory in 2 studies, and executive function, learning performance, and driving skill. However, its short-term intervention was not very effective and only 2 studies showed improvement in attention speed. Given the high heterogeneity between studies, more research is needed using more similar cognitive assessment tools for better conclusions.

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Nothing to declare

Authors' contribution

The first and second authors were more involved in this project than others. All authors participated in the preparation of the final version.

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Conflict of Interest

The authors declare that there is no potential conflict of interests in this review.

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