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Review

Potential of *Solanum betaceum* to improve cognition: A systematic review of animal studies

[Potencial de *Solanum betaceum* para mejorar la cognición: Una revisión sistemática de estudios en animales]

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Abstract

Context: *Solanum betaceum* is rich in bioactive compounds associated with various health applications, including plausible benefits on cognitive impairment caused by neurodegenerative diseases such as Alzheimer's disease (AD).

Aims: To investigate the potential benefit of consuming *S. betaceum* to alleviate cognitive and memory decline.

Methods: The review was conducted as a systematic review of an *in vivo* animal study. A search was performed of five databases using the keywords: "solanum betaceum", "S. betaceum", "tamarillo", "neurodegenerative diseases", "memory loss", "cognitive impairment". SYRCLE tool was used to assess the risk of bias. Data on the underlying molecular mechanisms of behavioral efficacy was additionally collected.

Results: A total of 66 journals were retrieved from the databases, resulting in 3 eligible studies. All included studies used albino rats as an AD animal model that were accustomed to laboratory conditions for about a week prior to the disease induction. In two studies, aluminum chloride ($AlCl_3$) was utilized to induce memory deficit, while another study used cigarette smoke. The result indicated that *S. betaceum* contained compounds such as phenolic and anthocyanin, which were plausibly responsible for the positive cognitive outcomes through molecular interaction with intracellular signaling protein cascades associated with anti-inflammation, brain oxygenation, synaptic plasticity, and cell viability. Further preclinical studies are needed to confirm these potentials.

Conclusions: This systematic review of the current evidence on the behavioral and biological influences of *S. betaceum* administration on AD animal models pointed out that the fruit might improve cognitive performance and prevent cognitive deterioration raised by several neurotoxins.

Keywords: antioxidants; Alzheimer's disease; cognition; systematic review; *Solanum*.

Resumen

Contexto: *Solanum betaceum* es rico en compuestos bioactivos asociados con diversas aplicaciones para la salud, incluyendo beneficios plausibles sobre el deterioro cognitivo causado por enfermedades neurodegenerativas como la enfermedad de Alzheimer (EA).

Objetivos: Investigar el beneficio potencial del consumo de *S. betaceum* para aliviar el deterioro cognitivo y de la memoria.

Métodos: La revisión se realizó como una revisión sistemática de un estudio in vivo en animales. Se realizó una búsqueda en cinco bases de datos utilizando las palabras clave: "solanum betaceum", "S. betaceum", "tamarillo", "enfermedades neurodegenerativas", "pérdida de memoria", "deterioro cognitivo". Se utilizó la herramienta SYRCLE para evaluar el riesgo de sesgo. Además, se recopilaron datos sobre los mecanismos moleculares subyacentes de la eficacia conductual.

Resultados: Se recuperó un total de 66 revistas de las bases de datos, lo que dio lugar a 3 estudios elegibles. En todos los estudios incluidos se utilizaron ratas albinas como modelo animal de EA, acostumbradas a las condiciones de laboratorio durante aproximadamente una semana antes de la inducción de la enfermedad. En dos estudios se utilizó cloruro de aluminio ($AlCl_3$) para inducir el déficit de memoria, mientras que en otro se empleó humo de cigarrillo. Los resultados indicaron que *S. betaceum* contenía compuestos como fenoles y antocianinas, que eran plausiblemente responsables de los resultados cognitivos positivos a través de la interacción molecular con cascadas de proteínas de señalización intracelular asociadas a la antiinflamación, la oxigenación cerebral, la plasticidad sináptica y la viabilidad celular. Se necesitan más estudios preclínicos para confirmar estos potenciales.

Conclusiones: Esta revisión sistemática de la evidencia actual sobre las influencias conductuales y biológicas de la administración de *S. betaceum* en modelos animales de EA señaló que el fruto podría mejorar el rendimiento cognitivo y prevenir el deterioro cognitivo suscitado por varias neurotoxinas.

Palabras Clave: antioxidantes; enfermedad de Alzheimer; cognición; revisión sistemática; *Solanum betaceum*.

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INTRODUCTION

Neurodegenerative disease (ND) will become a major concern for medicine and public health in the next years because of global demographic changes (Logroscino and Tortelli, 2015). The global care for chronic neurodegenerative illnesses is also expensive and has logistical limits (Di Paolo et al., 2019). The deteriorating impacts of the diseases on the quality of life of patients, caregivers, and overall world socioeconomics are alarming (Maresova et al., 2020). Nonetheless, several clinical concerns over natural product usage in preventing and treating NDs have arisen (Van Schependom and D'Haeseleer, 2023). Yet, there is still a lack of scientific support or evidence for their efficacy and patient safety.

The most prevalent ND, Alzheimer's disease (AD), has become a major cause of dependency in the elderly worldwide, with the number of cases estimated to have reached 50 million (WHO, 2023). The Alzheimer's Association Report (2020) also showed an increase of 10 million AD cases every year. Cognitive impairment in AD is a manifestation of a series of changes in the brain. It initially starts with forming extra- and intraneuronal amyloid plaques (Aminoff et al., 2015). The extracellular deposits of amyloid-β (Aβ) form neuritic plaques, which affect physiological neurochemical signaling in the brain, one of which is the N-methyl-D-aspartate (NMDA) receptor (De Strooper and Karran, 2016).

Aβ plaque has been hypothesized to cause sustained Ca^{2+} influx by dysregulating NMDA receptor (NMDAR), causing activation of proteases such as calpains (Liu et al., 2019; Tanqueiro et al., 2018). This protease breaks the brain-derived neurotrophic factor (BDNF) signaling by truncating the BDNF main receptor, the full-length isoform of the tropomyosin receptor kinase B (TrkB) receptor. The binding between the TrkB receptor and BDNF is particularly important in long-term potentiation (LTP) and synaptic growth (Tanqueiro et al., 2018). Disturbance in this signaling pathway causes synaptic loss in the whole cortical area, including the hippocampus, which plays an important role in the decline of memory capacity in AD (Tanqueiro et al., 2018; Kazim and Iqbal, 2016).

S. betaceum, known as tamarillo or tree tomato, contains various important bioactive compounds, including anthocyanins and phenolics, both known as antioxidant agents, which are potentially beneficial as adjuvant therapy for AD (Diep et al., 2020; Safitri et al., 2019). The anthocyanin level in the dried pulp ranges from 102.4-168.9 mg/100 g, higher than other fruits with similar colors (Diep et al., 2020; Espin et al., 2016). The phenolic content ranged from 2.43-6.18 g/100 g dry weight with hydroxycinnamoyl derivatives as the dominant substances (60.25-421.55 mg/100 g dry weight), making its antioxidant capacity stronger than apples, kiwi, red grapes, and oranges (Acosta-Quezada et al., 2015; Espin et al., 2016).

Recent animal study has shown that the antioxidants of *S. betaceum* are promising natural medicines that may have the benefit of slowing or preventing AD progression with fewer side effects than synthetic drugs (Safitri et al., 2019). However, no study has currently described the consistency of such promising results. Therefore, this review aims to be the first systematic review of all animal studies that investigated the potential of *S. betaceum* to alleviate cognitive and memory impairment represented through behavioral effects and biological influences in AD animal models.

MATERIAL AND METHODS

Eligibility criteria

Study eligible for the current review was the trial working with (i) the population of neurodegenerative disease-affected animals, (ii) intervened by *S. betaceum*, (iii) as compared to those without, (iv) observing the outcome if there is a cognitive improvement. The specific inclusion criteria were (i) an *in vivo* animal study, (ii) using a randomized controlled trial design, (iii) administration of *S. betaceum* extract by any route, and (iv) behavioral cognitive tests as the primary outcome. Research with irrelevant topics and incomplete manuscripts would be excluded from this review. Any studies categorized as conference abstracts, journals, oral communications, or textbooks were excluded during the selection process.

Information sources

The reviewers searched articles and extracted data from studies that met the criteria. Studies were retrieved on PubMed, Scopus, ScienceDirect, Proquest, and Web of Science with the keywords: "solanum betaceum", "S. betaceum", "tamarillo", "neurodegenerative diseases", "memory loss", "cognitive impairment". Boolean operators (OR and AND) were applied to expand and narrow search results. There was no year-publication limitation. To limit the occurrence of undesirable articles, these keywords and MeSH terms were searched in the "Title/Abstract" category.

Search strategy

The first three reviewers independently searched the database as well as literature identified through other sources in Rayyan (http://rayyan.qcri.org), a

web-based platform to expedite the initial screening of abstracts and titles incorporating a high usability level as it filters duplicates. The searches can be exported from the databases to Rayyan in "txt" and "ris" formats. The reviewers also independently screen the abstracts obtained against predetermined criteria in this tool. In more detail, the type of experimental animal, type of intervention, and outcome assessed will be evaluated during the selection process. Any disagreements were reached by consensus among other authors.

Selection process

All the included studies were appraised in three stages to collect the necessary data. The first stage involved summing up the general information concerning the year of publication, country, and the period in which the research was conducted. In the second stage, every article was appraised concerning the animal study design, how to get animals used to a laboratory environment, and how to induce cognitive loss in experimental animals. In the final part, the reviewers interpret the cognitive and behavioral results of the experimental animals qualitatively and quantitatively. The outcome is ultimately selected from the majority of occurrences. Any processes for obtaining or confirming data from study investigators.

Data collection process and the items

The first three reviewers will seek out the data from the included studies. The outcome, particularly, will be grouped into the identity, which includes authors, year of publication, and country where the research took place. The next group of data contains the characteristics of each study, including the type and number of experimental animals, the agent used to induce neurodegenerative disease, the dose, and the duration of exposure. From the two intervention and control groups, the results of each variable group will be extracted in the form of their time point from each memory evaluation method. Finally, conclusions will be drawn based on what is written in the manuscript and approved by the current reviewer.

Study risk of bias assessment

The included studies were further assessed for methodological quality using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) to score the risk of bias (Hooijmans et al., 2010; 2014). This process is carried out by one of the two reviewers independently and will then be discussed with other reviewers before proceeding to the next stage.

Effect measures, synthesis methods, reporting bias assessment

Online data processing, Google Sheets, will be used to tabulate the data. This tool was chosen because it can be accessed jointly by reviewers so that all reviewers can correct data synthesis results to minimize errors. A meta-analysis may only be carried out if the number of studies is sufficient and there are differences between studies or high heterogeneity.

Certainty assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the quality of evidence and strength of recommendations of each study. The GRADE approach is suitable for SR of animal studies with three criteria that level up the rate i.e., large magnitude of impact, dose-response gradient, and plausible confounding (Wei et al., 2016). With the aid of GRADEpro-GDT web tools, five criteria—risk of bias, indirectness, inconsistency, imprecision, and publication bias—are used to rate the evidence (Guyatt et al., 2011a-f).

RESULTS

Study selection

A total of 65 journals were retrieved through databases, namely PubMed (n = 1), Scopus (n = 22), ScienceDirect (n = 19), Proquest (n = 21), Web of Science (n = 2), and one was identified outside the database. A screening process from the abstract was performed to exclude records based on criteria, e.g., the publication type, non-trial or non-animal subject, different interventions, and outcomes presented. Thus, only three completed studies were eligible for further assessment. The selection process for related studies was carried out based on the criteria shown in Fig. 1.

Study characteristics

Characteristics of the three studies are presented in Table 1. In short, three included studies in this systematic review used albino rats as the experimental animals. The weight of the rat varied from 150 to 200 g. Rats were accustomed to laboratory conditions for about a week prior to the disease induction. There were no food and water restrictions throughout the experiments.

Risk of bias in studies

The evaluation based on the SYRCLE quality assessment showed several potential risks of bias (Table S1). Firstly, the sample size differences were observed with no calculation method reported in the study. The behavioral effect was based on post-intervention

Table 1. Characteristics and outcomes of included studies.

Author	Animal study (Sex)	Outcome type	Cognitive induction agent	Control		Intervention						Outcome
				N	Mean (s)	Time	Duration (days)	*S. betaceum* (mg/kg BW)	N	Memory evaluation method	Mean (s)	
Safitri et al. (2019)	Albino rats (NM)	Posttest only	$AlCl_3$ 2g/L for 21 days	10	35.71	21 days post $AlCl_3$ induction	14	100	10	MWM	15.85	A decrease in escape latency of the MWM test in $AlCl_3$-induced rats was observed significantly. A higher NMDAR level in the control group compared to the intervention group, as well as a significant increase in the intervention group observed concomitantly with an increasing dose of *S. betaceum*.
								200	10		15.57	
								400	10		16.71	
Kengne et al. (2019)	Albino rats (NM)	Posttest only	$AlCl_3$ 4.2 mg/kg BW i.p. for 28 days	6	RAM	0.25	28	200 of *S. betaceum* extract	6	RAM	0.76	*S. betaceum* significantly increased the average time spent in the correct (baited) arms compared to the AlCl3-treated group by the RAM test. Furthermore, raw juice administration and 200mg/kg dose extracts obtained the best average time, respectively. Rats treated with *S. betaceum* extract and raw juice showed a significant reduction of the latency period, observed from the MWM test, compared to the untreated $AlCl_3$-exposed group.
					MWM	33.88				MWM	6.11	
								400 of *S. betaceum* extract	6	RAM	0.58	
										MWM	5.17	
								1 mL raw juice/200 g	6	RAM	0.68	
										MWM	5.64	
Khaerunnisa et al. (2019)	Albino rats (NM)	Posttest only	Smokes exposure 3 cigarettes /day for 28 days	NM	23	During smokes exposure	28	100	NM	Y-maze	13.14	*S. betaceum* decreased time spent in Y-maze and increased hippocampal CREB and BDNF levels. Meanwhile, there was no significant difference in NMDA levels according to the Kruskal-Wallis test. The increased number of neurons, oligodendrocytes, microglia, and astrocytes in the hippocampus of the treated group was evaluated using hematoxylin-eosin staining.
								200			15.52	
								400			18.05	

NM: Not mentioned; CREB: Cyclic AMP-Response Element-Binding; BDNF: Brain-derived neurotrophic factor; MWM: Morris Water Maze; RAM: Radial 8-Arm Maze.

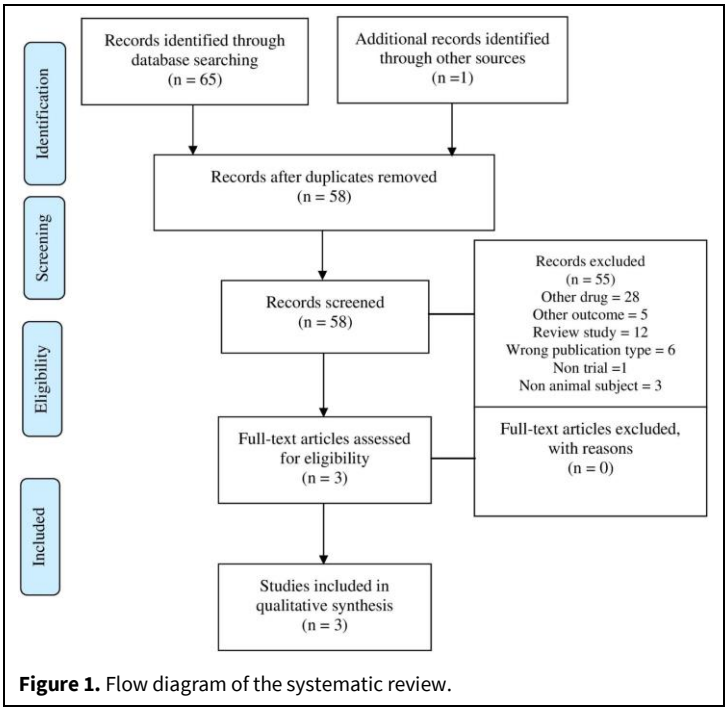

Figure 1. Flow diagram of the systematic review.

evaluation, while no information was given regarding the baseline cognitive function and the potential confounding factors such as motor speed and mobility. Furthermore, none of these studies mentioned blinding and sequencing randomization during intervention and outcome assessment.

Reporting biases and certainty of evidence

Due to the small number of studies, although the data is still feasible to synthesize, as well as the use of different types of exposure to experimental animals and the unclearness of the number of interposed animal models, it is not feasible to carry out a meta-analysis in the current review. However, the GRADE approach was utilized for appraising the certainty of evidence towards the outcome of all included studies, as shown in Table S2. It turned out that the time spent on mazes assessed a moderate certainty of behavioral outcome. This result was generated as the reviewers anticipated that the included study might not be comprehensive enough with all positive outcomes and a small sample size.

Results of individual studies

The experimental groups consisted of at least one cognitively healthy control group that did not receive *S. betaceum*, and another group that was induced into memory decline but did not receive *S. betaceum*. In contrast, the remaining groups received *S. betaceum* after or during cognitive impairment induction. Memory deficits were induced by injecting aluminum chloride ($AlCl_3$) in two studies, while another study used cigarette smoke.

Khaerunnisa et al. (2019) and Safitri et al. (2019) used a similar method to extract *S. betaceum* extraction. Both studies started out with drying *S. betaceum* using a fresh dryer, then proceeded to extract dry powder through maceration using ethanol solvent. Next, the extract was processed with filtration and evaporation with a rotary vacuum evaporator. Subsequently, the ethanol extract of *S. betaceum* was added to the subjects' diet as a suspension. On the other hand, Kengne et al. (2019) used two forms of *S. betaceum* dietary intervention: fruit extract and raw juice. In this study, fruit extraction was done with the following method: (1) Freshly harvested S. *betaceum* was washed, cut, and dried in an oven at 45°C with ventilation; (2) Dried fruits were finely grounded to a powder; (3) The obtained powder was soaked to specific solvents which were water, ethanol, and hydroethanolic mixture for 24 hours with gentle stirring; (4) The mixtures were filtered, then dried using an air oven at 45°C. The raw juice preparation was made by having the fruits washed, cut, and crushed into a paste, which would be put in a colander to obtain the raw juice.

Each study used different doses and had a different study design. Safitri et al. (2019) used five animal groups: the negative control group, the $AlCl_3$-induced control group, and three different intervention groups. Except for the negative control group, $AlCl_3$ was given for 21 days to induce memory impairment,

followed by oral administration of 100, 200, or 400 mg/kg BW of *S. betaceum* extract for another 14 days for the treatment groups.

Kengne et al. (2019) used six different groups: the normal animal group, the negative control group, the positive control group, and three different intervention groups. Except for the normal animal group, $AlCl_3$ was given daily along with the assigned treatment through the 28-day experimental course. The negative control group received no treatment, while the positive control group received 200 mg/kg BW vitamin C. The intervention groups received each 200 mg/kg BW *S. betaceum* extract, 400 mg/kg BW *S. betaceum* extract, or 5 mL/kg BW of raw juice.

As for the study by Khaerunnisa et al. (2019), four groups of rats were exposed daily to cigarette smoke to induce memory impairment, followed by either no treatment or oral administration of *S. betaceum* extract at 100, 200, or 300 mg/kg BW for each treatment group.

All three studies showed positive effects of *S. betaceum* on memory function. The significantly decreased escape latency in the Morris water maze (MWM) test, radial eight-arm maze (RAM), and Y maze were found compared to the control group. Additionally, Kengne et al. (2019) found that animals treated with raw juice and powder extract had a better average time of correct (baited) arm than the untreated animal group. Furthermore, they also found that raw juice preparations had the best average time spent in the correct (baited) arms during acquisition trials compared to extract preparations. However, no significant difference in the escape latency was found between the two different preparations.

The administration of *S. betaceum* leads to the alteration of brain protein levels. Khaerunnisa et al. reported an insignificant decrease in NMDA levels, while Safitri et al. (2019) reported a significant decrease. Moreover, Safitri et al. (2019) found that the level of BDNF remained similar across animal groups. The NMDA and BDNF levels were evaluated from hippocampus samples of the left or right hemisphere by the enzyme-linked immunosorbent assay (ELISA) method. Khaerunnisa et al. (2019) also assessed the number of neurons and glial cells by using histopathological approach.

In the study by Kengne et al. (2019), the total protein, catalase activity, malondialdehyde, and glutathione levels of the brain supernatant sample of the treatment groups increased relative to the non-treated group. The antioxidant activity of *S. betaceum* extract was evaluated in vitro using the 2,2-diphenyl-1-picryl-hydrazyl-hydrate, or DPPH method, by analyzing the free radical scavenging potential, confirming the higher antioxidant capacity of the ethanolic extract of *S. betaceum* compared to the aqueous and hydroethanolic extract yet lower than vitamin C.

DISCUSSION

The current review aimed to investigate the effect of *S. betaceum* on the memory capacity of a memory-impaired rat model. Additionally, the potential mechanisms of two bioactive compounds contained in *S. betaceum*, namely phenolics and anthocyanin, to prevent neurodegenerative processes are further elaborated. This review showed that the ethanol extract and raw juice of *S. betaceum* improved the learning and spatial memory of the animal model of memory deficit. Investigation of the biological mechanisms of action of the plant extract so far confirmed the substance's antioxidative effect, which may prevent oxidant-related neuronal injury. However, thorough experiments with improved methodologies are still required to reveal the biological pathways in administering the plant extract. Here, we described the putative biological roles of the phenolics and anthocyanin, two bioactive substances contained in *S. betaceum*, which may involve the underlying mechanisms of the cognitive benefits observed in this review, as shown in Fig. 2.

Maintaining neural viability and plasticity

Although the classical hydrogen-donating antioxidant activities of phenolics and anthocyanin have been attributed to their neuroprotective benefits, as shown in *in vitro* studies, the extensive metabolism of these molecules during absorption up to systemic circulation greatly reduces their concentration and antioxidant potential (Spencer, 2008; 2010; Winter and Bickford, 2019). Alternatively, several indirect strategies may play a role in managing cellular oxidative stress. Anthocyanin has been shown to upregulate the endogenous antioxidant molecule, glutathione, and the antioxidant enzymes such as catalase, glutathione peroxidase, and glutathione reductase (Kelsey et al., 2011; Neves et al., 2019). The modulation of the transcription factor protein, the nuclear factor erythroid 2-related factor 2 (Nrf-2) by anthocyanin is responsible for the enhanced gene expression of antioxidant-related enzymes (Hwang et al., 2011; Shih et al., 2007). Finally, the direct action of anthocyanin to maintain mitochondrial redox function and reduce mitochondrial oxidative stress may also mediate the neuroprotective effect of anthocyanin by mitigating cellular oxidative stress (Neves et al., 2019).

The neuroprotective effect of phenolics and anthocyanin can also occur through their pharmacological

interactions with several cellular signaling cascades which regulate neuronal survival, apoptosis, and plasticity. Phenolics and anthocyanin have high affinity to the adenosine triphosphate (ATP) binding sites of many signaling proteins, such as protein kinase C, phosphatidylinositol 3-kinase (PI3K), and protein kinase B (PKB/Akt) pathway, and mitogen-activated protein kinase (MAPK) family such as the extracellular signal-regulated protein kinase (ERK) (Spencer, 2007). In mature neurons, the activation of these cascades leads to the expression of the transcription factor cyclic AMP-response element-binding (CREB) protein and the production of neurotrophic molecules such as BDNF. This activation is important during memory formation and consolidation, promotes synaptic plasticity, and prevents pro-apoptotic molecules such as bad and caspases from being activated. Furthermore, the inhibitory effect of phenolics and anthocyanin on the c-Jun N-terminal kinases (JNK), apoptosis signal-regulating kinase-1 (ASK-1), and p38-mitogen-activated protein kinase (p38-MAPK) pathways are associated with increased neuronal survival (Vanzour et al., 2021).

Phenolics and anthocyanin maintain synaptic function by inducing neural spine density, morphology, and motility increases. These architectural changes lead to enhanced synaptic connectivity and synaptic communication between neurons. Direct interaction between phenolics and MAPK as well as protein kinase A (PKA) protein cascades is responsible for such changes (Matsuzaki et al., 2008). Furthermore, another study indicated that phenolics and anthocyanin were able to maintain the physiological concentration level of synaptic proteins, both the presynaptic synapsin and synaptotagmin 1 (SYT-1), as well as the postsynaptic CaMKII protein after oral administration of phenolics and anthocyanin (Liu et al., 2017; Wang, 2008).

Suppressing protein aggregation, neuroinflammation, and calcium homeostasis

Another plausible neuroprotective mechanism of *S. betaceum* may be gained through the role of phenolics and anthocyanin as anti-inflammatory agents. Several studies have demonstrated phenolics and anthocyanin to attenuate the expression of pro-inflammatory molecules and cytokines such as nitric oxide, interleukin-1B, and tumor necrosis factor (TNF-α) in glial cells. Inhibition of several pro-inflammatory regulatory proteins like JNK and p38-MAPK by phenolics and anthocyanin prevents the activation of the nuclear factor-κB (NF-κB), a transcription factor, which is responsible for the expression of many pro-inflammatory genes (Amin et al., 2017; Kim et al., 2017).

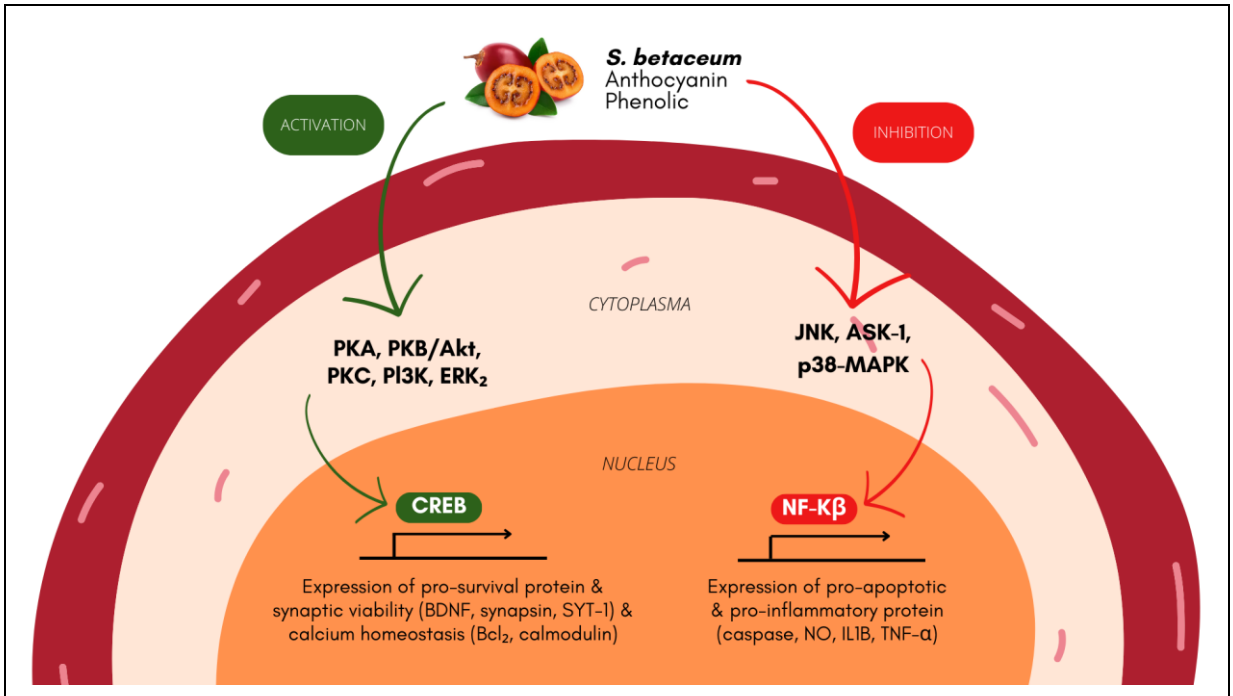

Figure 2. Putative biological pathways resulted in the cognitive benefits of *Solanum betaceum* consumption.

PKA: protein kinase A, PKB/Akt: protein kinase B, PKC: protein kinase C, PI3K: phosphatidylinositol 3-kinase, ERK2: extracellular signal-regulated protein kinase, CREB: Cyclic AMP-Response Element-Binding, BDNF: Brain-derived neurotrophic factor, SYT-1: Synaptotagmin 1; Bcl2: B-cell lymphoma 2; JNK: c-Jun N-terminal Kinases, ASK-1: apoptosis signal-regulating kinase-1; p38-MAPK: p38-mitogen-activated protein kinase; NFkB: Nuclear Factor Kappa-B; NO: Nitric Oxide; IL1B: Interleukin 1 Beta; TNFa: Tumor Necrosis Factor Alpha.

Phenolics and anthocyanin prevent protein aggregation and stimulate autophagy. Several studies using fruit extract or pure anthocyanin reported reduced accumulation of toxic oligomerized proteins such as amyloid-B, a pathological hallmark of AD. The activation of the mammalian target of rapamycin (mTOR) protein cascade by phenolics and anthocyanin is responsible for the enhanced production of autophagosomes and accelerates cellular protein homeostasis (Moosavi et al., 2015; Squillaro et al., 2018; Uddin et a., 2020).

Finally, the role of anthocyanin and phenolics in intracellular calcium homeostasis may also contribute to the observed positive cognitive outcomes. Excitatory stimuli such as NMDA induce massive calcium influx, leading to mitochondrial dysfunction and the activation of calcium-dependent pro-death factors such as calpains (Soriano et al., 2008). Anthocyanin and phenolics were reported to maintain physiological intracellular calcium concentration by upregulating the expression of intracellular calmodulin and B-cell lymphoma 2 (Bcl2), which are important in preserving intracellular free calcium levels (Meng et al., 2018).

Finally, the effect of phenolics and anthocyanin in increasing cerebral oxygenation should be taken into account as the possible mechanistic route by which *S. betaceum* improves cognition. Several human studies demonstrated that phenolics-anthocyanin-rich substance consumption was associated with increased cortical oxygenation and followed by improved cognitive performance (Gratton et al., 2020; Jackson et al., 2020; Williams et al., 2017).

Limitations of current studies and implications

While current studies showed the cognitive benefit of dietary *S. betaceum* in animal models of impaired cognition, studies on the underlying mechanisms behind the behavioral effect are still lacking. The recent state of evidence has confirmed the antioxidative effect of the fruit in one study. However, the other possible mechanisms described above are not yet confirmed. Two included studies also showed that the oral *S. betaceum* intake prevented the concentration reduction of two proteins, CREB and BDNF, induced by protein exposure. Those results should be cautiously interpreted since hippocampal samples used in these studies were fixated, which caused the protein assay to become inaccurate. Furthermore, one study tried to show the effect of *S. betaceum* intake on neuronal and glial cell viability in the hippocampus. However, manual cell quantification using unspecific morphological histological staining was deployed, which is unreliable to distinguish across cell types and assess cell viability. More reliable approaches using cell-specific markers should be used, such as the automated flow cytometry or the manual isotropic fractionator counting method based on fluorescence microscopy (Collins et al., 2010).

Another limitation of the current studies is the interpretation of the biochemical assays used. Two studies that reported the results of NMDA concentration assessment, referring to the reported assay kit, interpreted the value as the level of NMDAR expression. While NMDAR assay is important due to its role in intracellular calcium intake and neurotoxin-induced excitotoxicity, interpretation of this protein should be based on the measure of the protein itself. Thus, the reported methodology in the current studies is still lacking, especially in brain sampling, including the fixation method and the biochemical assays. Moreover, the studies found were limited to only three studies. It might be caused by the limited search engines, resulting in a minimal sample size during the data review process and impacting limited results according to the studies obtained. However, further preclinical studies using sound methodologies and clear reporting are needed. More standardized studies with resemblant outcomes would be expected to investigate the putative mechanisms by which this compound is cognitively beneficial

CONCLUSION

Based on studies in rats, the administration of *S. betaceum* can improve cognitive function and prevent cognitive deterioration induced by various neurochemical toxins. The effects of the natural compound as an antioxidative agent have been indicated. However, more studies using sound methodologies and clear reporting are required to investigate the putative mechanisms by which this compound is cognitively beneficial. These mechanisms include the potential benefits of cellular viability, neuroinflammation, synaptic function, and brain oxygenation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Imania HAN	Rachma AF	Kurniawati LA	Hidayati HB	Wungu CDK	Nazmuddin M
Concepts or ideas	x	x	x	x	x	x
Design	x	x	x			x
Definition of intellectual content	x	x	x	x	x	x
Literature search	x	x	x		x	x
Experimental studies	x	x	x			
Data acquisition	x	x	x			
Data analysis	x	x	x			
Manuscript preparation	x	x	x		x	x
Manuscript editing	x	x	x		x	x
Manuscript review	x	x	x	x	x	x

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Supplementary data

Table S1. Risk of Bias: SYRCLE (the SYstematic Review Centre for Laboratory animal Experimentation).

Questions	(Safitri et al., 2019)	(Kengne et al, 2019)	(Khaerunnisa et al., 2019)
Was the allocation sequence adequately generated and applied?			
Did the investigators describe a random component in the sequence generation process?	U	U	U
Were the groups similar at baseline or were they adjusted for confounders in the analysis?			
Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?	Y	Y	U
If relevant, did the investigators adequately adjust for unequal distribution of some relevant baseline characteristics in the analysis?	-	-	-
Was the timing of disease induction adequate?	Y	Y	Y
Was the allocation to the different groups adequately concealed?			
Could the investigator allocating the animals to intervention or control group not foresee assignment?	U	U	U
Were the animals randomly housed during the experiment?			
Did the authors randomly place the cages or animals within the animal room/facility?	U	U	U
Is it unlikely that the outcome or the outcome measurement was influenced by not randomly housing the animals?	U	Y	U
Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?			
Was blinding of caregivers and investigators ensured, and was it unlikely that their blinding could have been broken?	U	U	U
Were animals selected at random for outcome assessment?			
Did the investigators randomly pick an animal during outcome assessment, or did they use a random component in the sequence generation for outcome assessment?	U	U	U
Was the outcome assessor blinded?			
Was blinding of the outcome assessor ensured, and was it unlikely that blinding could have been broken?	-	-	-
Was the outcome assessor not blinded, but do review authors judge that the outcome is not likely to be influenced by lack of blinding?	U	U	U
Were incomplete outcome data adequately addressed?			
Were all animals included in the analysis?	U	U	U
Were the reasons for missing outcome data unlikely to be related to true outcome? (e.g., technical failure)	U	U	U

Table S1. Risk of Bias: SYRCLE (the SYstematic Review Centre for Laboratory animal Experimentation) (continued...)

Questions	(Safitri et al., 2019)	(Kengne et al, 2019)	(Khaerunnisa et al., 2019)
Are missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups?	U	U	U
Are missing outcome data imputed using appropriate methods?	U	U	U
Are reports of the study free of selective outcome reporting?			
Was the study protocol available and were all of the study's pre-specified primary and secondary outcomes reported in the current manuscript?	-	-	-
Was the study protocol not available, but was it clear that the published report included all expected outcomes (i.e. comparing methods and results section)?	U	Y	U
Was the study apparently free of other problems that could result in high risk of bias?			
Was the study free of contamination (pooling drugs)?	Y	Y	Y
Was the study free of inappropriate influence of funders?	Y	Y	Y
Was the study free of unit of analysis errors?	Y	Y	Y
Were design-specific risks of bias absent?	Y	Y	Y
Were new animals added to the control and experimental groups to replace drop-outs from the original population?	-	-	-
Conclusion	Low risk	Low risk	Unclear

Table S2. Certainty of Evidence: GRADE (Grading of Recommendations, Assessment, Development, and Evaluations).

Certainty assessment						**No. of patients (%)**		**Effect**		**Certainty**
No of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	***S. betaceum* extract**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**	
3	randomised trials	not serious	not serious	not serious	not serious	14/28 (50.0%)	8/8 (100.0%)	not estimable	not estimable	⨁⨁⨁⨁ High

CI: confidence interval.