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Nutraceutical Potential for Alzheimer's Disease Treatment

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Cover Page Footnote

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NUTRACEUTICAL POTENTIAL FOR ALZHEIMER'S DISEASE TREATMENT

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ABSTRACT

Alzheimer's disease (AD) is a progressive disorder involving buildup of excessive amounts of proteins such as beta amyloid in the brain that leads to memory loss, inability to perform daily functions, and an early death. By 2060, the number of cases is forecast to nearly triple current numbers. Age is the primary risk factor for AD and no new drugs have been approved since 2003. Nutraceuticals, a broad category of substances that can be utilized for both medicinal and nutritional purposes may be able to help, which is why they are being more widely researched. Overall, a number of attempts to use isolated nutrients such as vitamins have failed to display in showing any improvement in AD. In fact, some of them have even worsened the disease, and the ones showing major improvements had some methodological flaws. However, isolated non-nutritive antioxidants and peptides exert some beneficial effects *in vitro*, *in vivo*, and in clinical trials, while non-isolated whole food extracts and melatonin show potential in clinical trials. Unfortunately, no known treatment can reverse disease progression, though some can slow it. Most of the treatments covered in this article had few side effects. Future research could combine some of these treatments and provide a possible natural prevention/treatment option for AD.

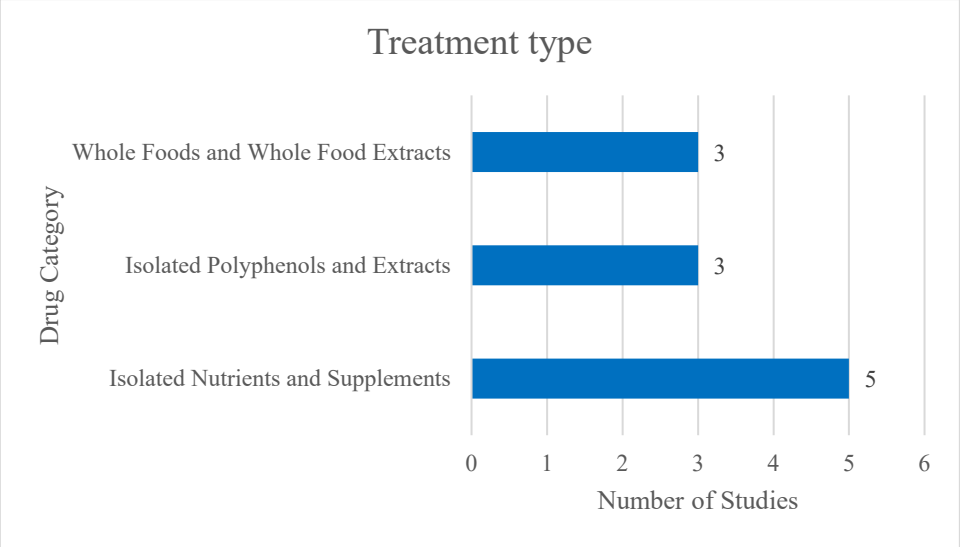
INTRODUCTION

Alzheimer's disease (AD) is a progressive disorder characterized by the buildup of excessive amounts of certain proteins in the brain that lead to memory loss, inability to perform daily functions, and eventual death. It is believed to affect approximately 5.5 million Americans, and usually becomes noticeable in the seventh decade of life. (1). For those at risk, age is the primary risk factor, with an exponential increase in incidence after 65. Certain genes, diet, and high blood pressure and cholesterol may also augment disease risk. (2). Recent advances in medical technology have enabled detection of the disease before serious symptoms arise, defined as preclinical AD. This is important because earlier treatment is likely to be more effective at stalling AD symptoms. However, it is difficult to define the beginnings of preclinical AD, since there is contention as to whether it should be diagnosed at the first signs of cognitive decline or biomarkers from lab results (3). A definitive AD diagnosis requires postmortem autopsy (4). Attempts to develop drugs to delay or treat AD have been mostly unsuccessful, with no new drugs having been approved since 2003. A number of them tried to target the beta-amyloid plaques that form in the brain, which is the hallmark symptom of the disease. As of early 2019, 132 agents were in clinical trials for AD (5). Since most of the synthetic chemotherapeutics have side effects, focus has been directed towards use of nutraceuticals, including curcumin, ginger, garlic, and essential oils, which have been used as traditional medicines in certain cultures.

Nutraceuticals are a broad category of substances that can be utilized for both medicinal and nutritional purposes. Lately, they have been more widely explored for medical research due to the belief that they may harbor potential to treat a wide array of chronic diseases. For example, an antioxidant found in certain foods called quercetin can prevent LDL-C cholesterol oxidation in

blood vessel endothelia, acting like a sponge soaking up free radicals (6). Genetics can also play a role in developing AD. It is surmised that certain dietary components can impact how genes associated with AD and other diseases are expressed, though few papers have examined this. Most of the nutraceuticals that have been examined are compounds derived from edible plants, such as catechins, resveratrol, and flavanols (7). Therefore, it may be worthwhile to search for a specific food, compounds isolated from food, or a combination of natural and/or synthetic drugs that can treat or reverse AD. Most research is currently done using isolated compounds. (Figure 1).

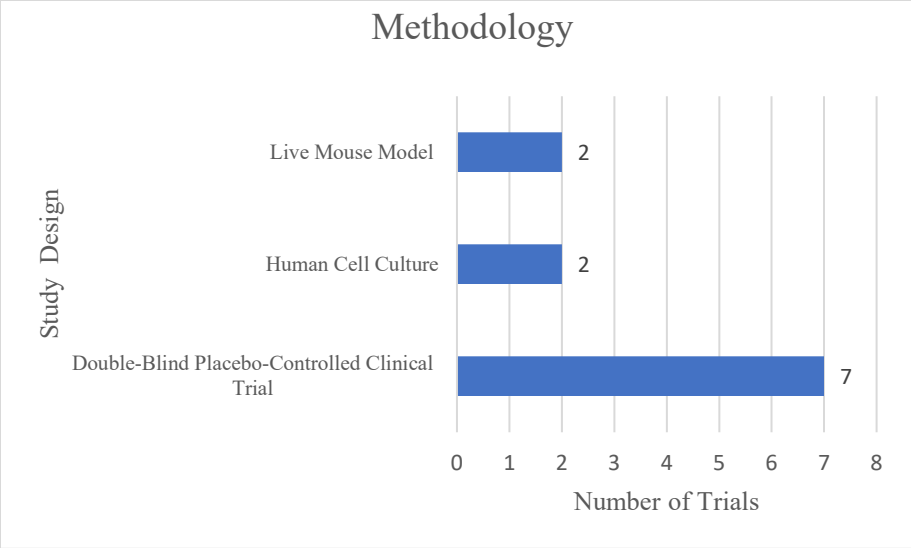
Figure 1:Research articles on different food items used to treat AD



AD cases are expected to increase from approximately 5 million to 13.9 million in 2060 (8). Some potential epigenetic targets are DNA and histone methylation, acetylation, and phosphorylation, since memory formation at least partially depends on these chemical reactions. This is supported by the observation that most cases of AD are not associated with known genetic mutations and present late in life. If familial genetic mutations were the sole cause, it would be possible to identify future AD patients from birth (9).

Quercetin, found in apples and onions, among other foods, can prevent the death of endothelial cells by protecting them from oxidative stress (6). Crocin, a compound found in Saffron, was found to minimize the deleterious effects of long-term stress on memory and learning (10). Multiple other compounds described in this review had positive effects in rodents but had failed to demonstrate those same effects in human randomized clinical trials. Quercetin and saffron are explored later. Figure 2 shows the study design of trials reviewed in this article.

Figure 2: Biological models used with nutraceuticals in AD. Randomized double-blind placebo-controlled study design is the most conclusive.



ISOLATED NUTRIENTS AND SUPPLEMENTS TO TREAT AD

Nutraceuticals can fall into several distinct categories. This can include food, food components, and vitamins (11). Limited research suggests sleep deprivation and AD exacerbate one another (12). Melatonin is a hormone that is chiefly released to induce the body to fall asleep. To explore whether melatonin supplementation improved symptoms, a formula that releases melatonin slowly was developed because the body normally metabolizes excess melatonin quickly. This double-blind placebo-controlled trial found that treatment resulted in an improvement in the ability for patients to carry out daily activities as well as sleep quality, though other aspects of AD were mostly unchanged (13). Thus, adding slow-releasing melatonin to other treatments may help patients with mild to moderate disease progression.

Docosahexaenoic acid (DHA) is an integral lipid in the brain. Preformed DHA can be found in fish and supplements, but humans can also synthesize it from Alpha-linolenic acid (ALA), found in vegetable oils, and fortified foods are available. Variations in blood levels partially depend on differential consumption of these sources (14). Unsurprisingly, increased intake is associated with a reduced risk of AD. In this double-blind trial, 402 patients without severe disease progression were randomized to either 2 grams of DHA daily or placebo. In animal studies, DHA had shown potential to treat some symptoms, but this trial found no beneficial effects. The researchers did suspect that DHA might still be beneficial if taken before clinical symptoms, that oxidation of DHA after consumption might limit its ability to benefit patients, and that certain genes may influence its effectiveness. (15). Unfortunately, in 2014, when 47 different omega 3 supplement brands were sampled to determine the actual quantities of the stated active ingredients, there was extensive variation in the levels of DHA and other lipids, with most containing less than stated on the labels (16). Accordingly, concerns over whether some DHA supplements contain the levels described on the labels are valid.

N-Palmitoylethanolamide (PEA) is a lipid commonly found in soy lecithin, egg yolks, and peanuts that controls other processes. Preclinical evidence suggests that it is very safe and can be used to treat atherosclerosis, inflammation, and pain, and some in vitro evidence suggests that PEA has the ability to attenuate some of the harmful effects of beta amyloid, including astrogliosis and neuroinflammation. In certain strains of live mice, PEA inhibited reactive gliosis and nutritionally supported neurons (17). Unfortunately, there is no human clinical evidence for the efficacy of PEA in the treatment of individuals with AD because not much is known about its pharmacokinetics, though one study found that ultra-micronized PEA could slow the progression of Parkinson's disease (18). Accordingly, more research on this compound's metabolism and subsequent clinical trials are needed to determine if it has potential for treatment of AD.

Previously, a phase I clinical trial had been done on supplementation of a combination of folate, alpha tocopherol, vitamin B12, two modified amino acids and acetyl-L-carnitine, which safely ameliorated some symptoms of dementia. This phase II double-blind placebo-controlled clinical trial with the same ingredients found that after 3 and 6 months, respectively, there were marked improvements in multiple measures of cognitive function, but these were accompanied with large standard errors, and these effects were limited to patients with mild to moderate dementia. Following this was an open-label extension, and those who had received placebo previously had cognitive improvement approaching levels comparable to the treated group in the blinded portion of the trial. Nutritional status was not measured, and patients were not separated into categories reflecting this, though it is mentioned that if this had been done, the beneficial effects of the treatment may have been cancelled out by any remaining damage from malnutrition in those with poor nutritional status (19).

In a double-blind placebo-controlled trial examining effects on AD markers, 78 participants were given either Vitamin E, C, and ALA, only Coenzyme Q, or a placebo. In the group taking all three supplements, there was a decrease in cognitive function despite a coinciding decrease in oxidative stress markers, and no effect on markers of tau proteins. This raises concerns for future trials involving isolated nutrients and antioxidants for AD treatment, particularly since treatment will need to be administered long-term to see regression of the disease (11). It is also possible that drugs in isolation simply are incapable of having a dramatic effect on AD beyond correcting deficiencies.

ISOLATED POLYPHENOLS AND EXTRACTS FOR AD TREATMENT

Curcumin, the yellow pigment of the spice turmeric has traditionally been used to treat a wide variety of disorders, has a multitude of medicinal properties, and is extremely cheap and safe, resulting in its status as the most studied compound as of 2015 (20). Curcumin is poorly absorbed, so it has been difficult to conduct clinical trials with it. However, it has some naturally occurring variants or analogues including bisdemethoxycurcumin, which has been demonstrated to exert stronger anti-inflammatory effects in rats. In blood cells of AD patients, curcumin dissolves some beta amyloid plaque (21). Future research could be done on curcumin, bisdemethoxycurcumin, and other analogues in humans.

Quercetin has been proposed to cross the blood brain barrier, allowing it to target the pathologies of AD (22). A strain of aged mice that had accumulated a buildup of tau proteins were

treated with quercetin, and no deleterious side-effects were observed. Additionally, it protected neurons in the inferior portion of the hippocampus, and reversed buildup of beta amyloid and tau proteins. It also showed a tangible improvement in memory and spatial learning and an apparent reduction in anxiety (23).

Colostrinin is a patented polypeptide rich in proline isolated from colostrum. It has been demonstrated in a small-scale trial to help treat AD patients by improving their social capabilities, mood, and motivation at 100 micrograms every other day. Neuroprotection was also conferred for human neuroblastoma cells mixed with the amyloid. A possible mechanism is through reduction of stickiness of beta amyloids 1-40, but it might also lower the toxicity of beta amyloid itself by preventing beta-amyloid induced neural apoptosis. (24).

WHOLE FOODS AND FOOD EXTRACTS

Rice bran is traditionally used as a cheap byproduct to feed livestock and was broken down into small peptides to be investigated in a human neural cancer cell culture for activity against AD. Previous research on extracts from the bran reported a noticeable effect on cancer. The cells were first treated with amyloid to simulate AD then treated with the fractionated rice bran peptides. Toxicity from the beta amyloid was inhibited by up to 45% in the cells treated with both amyloid and peptides compared to those that were treated with amyloid alone, but complex molecular interactions make it difficult to establish a mechanism of action (25).

Saffron has the ability to combat cancer, inflammation, pain, atherosclerosis, hepatic damage, hyperlipidemia, and hypertension. Some clinical trials have shown that saffron possesses similar anti-AD properties as the conventional approved therapeutics such as Donepezil and Memantine, but with fewer and lesser side effects. Saffron has not been tried in combination therapies yet (26).

Green tea extract was used in a clinical trial conducted at Daejeon University Oriental Hospital in Korea. Amongst the study participants, 91 otherwise healthy people aged 40-75 years with memory complaints were randomized to either capsules with green tea extract and L-theanine or placebo capsules twice daily 30 minutes after meals. The green tea extract improved some measures of cognitive function, including color reading and an increase in theta brain waves, suggesting augmented mental performance, but only marginally. There were markedly more female participants than males, but it is unknown whether this affected the results. Additionally, as with the phase II clinical trial evaluating six isolated nutrients, the data could be put into a more useful context if nutritional status were established for each participant prior to the study (27).

CONCLUSION

Currently approved therapeutics for chronic conditions such as hypertension, pain, diabetes, etc. are associated with moderate to severe side effects. For example, statins, which are the standard hypercholesterolemia treatment can occasionally cause cause muscle pain and rhabdomyolysis (28). Compounds found in plant foods, such as curcuminoids and sterols, can lower cholesterol but have an impressive safety profile (29). They also have other beneficial effects (20). This has prompted further investigation into the use of nutraceuticals for the treatment of

AD. Overall, numerous attempts to use isolated nutrients such as vitamins have failed to show improvement. One trial using multiple supplements accelerated disease progression (11), and the ones showing major improvements had the limitation that nutritional status prior to the study was not evaluated (19, 25). Further research is necessary to investigate the extent of benefits provided by PEA and the beneficial combination of supplements found in one trial. Isolated non-nutritive antioxidants including curcumin and fractionated rice bran peptides exert some beneficial effects on disease progression *in vitro*, *in vivo*, and in clinical trials. Similarly, non-isolated whole food extracts and melatonin also show effectiveness in clinical trials. It is important to recognize that there is no known treatment that can reverse disease progression. Figure 3 provides a graphical representation of how the treatments affected disease progression. In addition, most of these treatments showed low toxicity and had few side effects. Research into nutraceutical use in the treatment of AD is still in its infancy, but the results from some of these trials are promising and warrant further investigation. Future research might be done on combinations of the most effective treatments today and replication of previous trials.

Figure 3

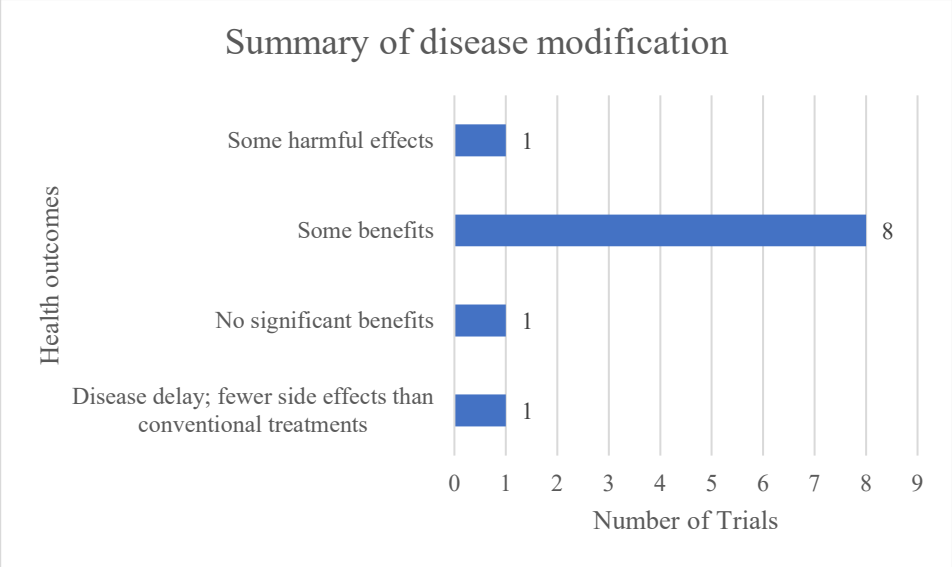


Figure 4: Summary of figures 1-3. Detailed table below figure.

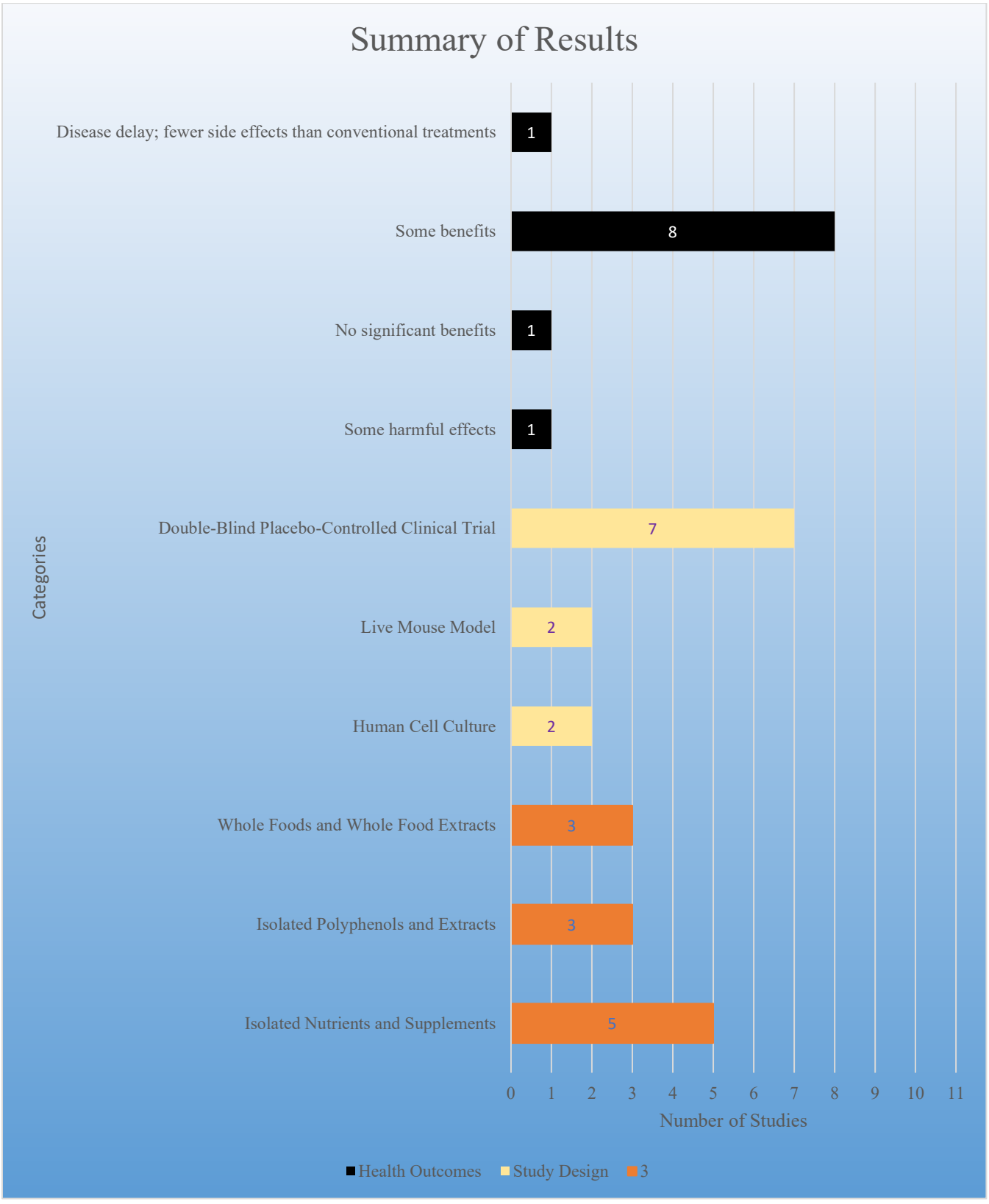


Table 1: Detailed summary of all the treatments categories, compounds, study designs, and published results. DBPCCT=double-blind placebo-controlled clinical trial, INS=isolated nutrients and supplements, IPE=isolated polyphenols and extracts, WF=whole foods and whole food extracts, MAA= modified amino acid, vit=vitamin, G=group

	Names	**Design**	**Result**
INS	Slow-release melatonin	DBPCCT	Some benefits
	Docosahexaenoic acid (DHA)	DBPCCT	No definite benefits
	N-Palmitoylethanolamide (PEA)	Live Mouse Model	Some benefits
	Combined: folate, vit E, vit B12, two MAAs and acetyl-L-carnitine	DBPCCT	Some benefits
	Combined: G1: Vitamin E, C, ALA G2: Coenzyme Q, G3: Placebo	DBPCCT	Some harmful effects
IPE	Curcumin	Human Cell Culture	Some benefits
	Quercetin	Live Mouse Model	Some benefits
	Colostrinin	DBPCCT	Some benefits
WF	Saffron	DBPCCT	Disease delay with fewer side effects than conventional treatments
	Green Tea Extract	DBPCCT	Some benefits
	Fractionated Rice Bran Peptides	Human Cell Culture	Some benefits

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