



Quantum and Tempus Theories of Functional Food Science: Establishment of dosage and time of consumption of functional food products

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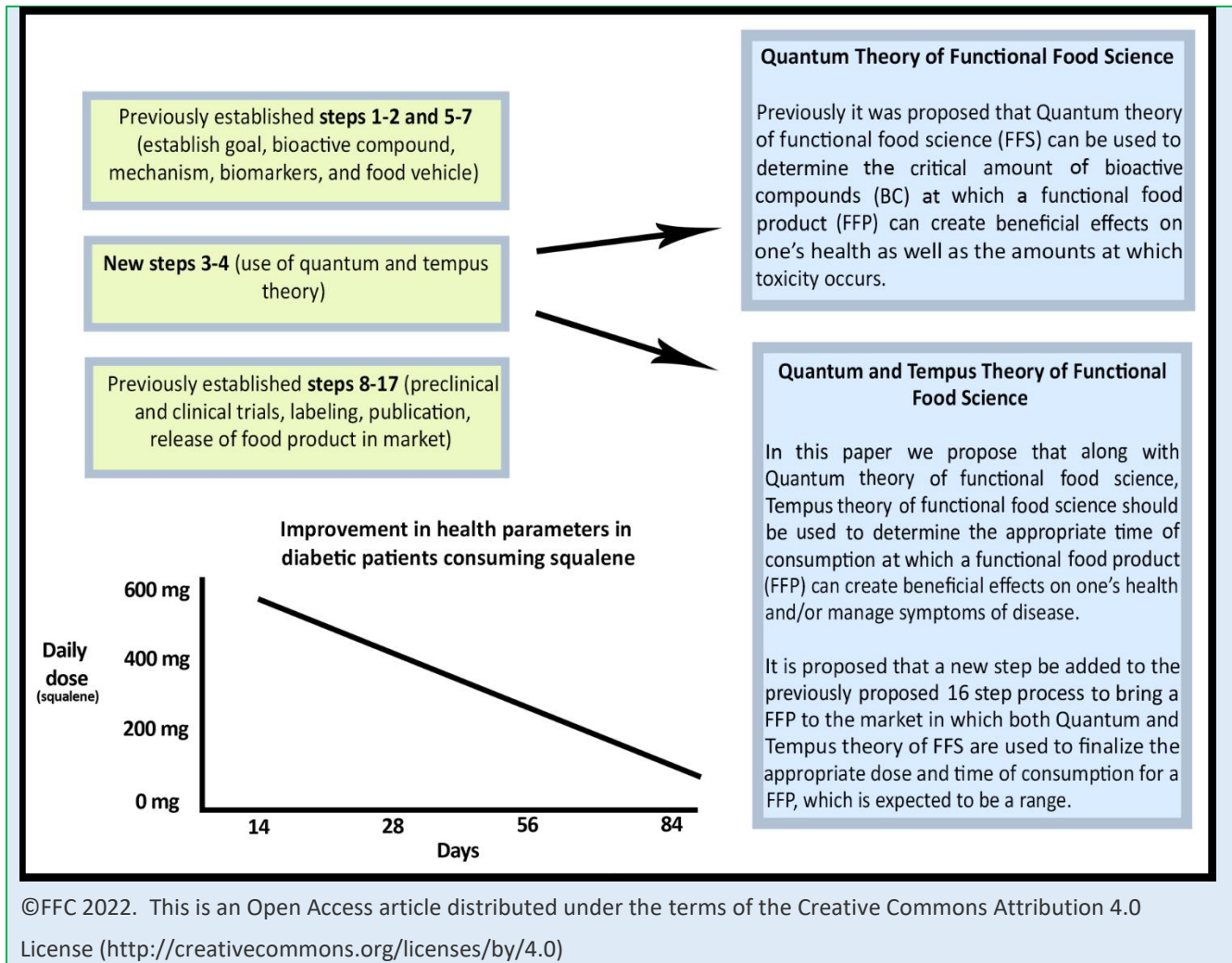
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ABSTRACT

In recent years, the United States has seen an increase in the prevalence of chronic diseases. There has also been an increased need in products that can prevent or manage symptoms of disease. Functional food products are food products that contain bioactive compounds that have been shown to produce beneficial effects that increase health. The Functional Food Center has created a 16-step process to develop and introduce functional food products to the market. As part of this process, researchers should establish the appropriate dosage of a bioactive compound, at which the product can be consumed safely and it can effectively improve health parameters. Previously, we suggested that Quantum theory of functional food science could be useful for finding the critical amount at which a bioactive compound will cause enough chain reactions to influence health and biomarkers of disease. In this paper, we propose that a new step be added to the 16-step functional food process, making the total amount of steps to 17. This new step should occur after establishing the appropriate dose and should focus on establishing the appropriate time of consumption using the Tempus theory of functional food science. The word, *Tempus*, comes from the Latin word for time. Similar to dosage, the time of consumption can impact the effectiveness of a bioactive compound, which is why this new step is important. Recent studies on diabetic patients have applied the Quantum and Tempus theories of functional food science to determine the appropriate range of dosage and time of consumption at which squalene, which is a bioactive compound belonging to the triterpene class, can improve parameters of health in diabetics. The studies found that consumption of squalene improves parameters of health in diabetic patients, however higher doses produced the effects in less time than lower doses. Although the studies were able to provide more information about the appropriate dose and time range for consuming the bioactive compound in that population, more research is needed to find the exact ranges.

Keywords: Functional food product, Bioactive compound, Dosage, Time, Quantum theory of functional food science, Tempus theory of functional food science



INTRODUCTION

In recent years, there has been an increase in the prevalence of chronic diseases, including Diabetes Mellitus, heart disease, and cancer. In the United States alone, a National Health Interview Survey conducted in 2018 found that 51.8% of adults had at least one chronic disease, with 27.2% of adults having two or more chronic diseases [1]. This is concerning for many health reasons, but an increase in prevalence of disease also comes with an increase in risk of mortality and health costs along with a decrease in quality of life [2]. With this increase in prevalence of disease, there has also been an increased

need for ways to prevent or manage them. Functional foods are products that have been proposed to be beneficial for growing health concerns, due to their health promoting properties.

Although there is not a formal definition for functional foods, the Functional Food Center (FFC) has proposed a definition for functional foods (FF) as “Natural or processed foods that contain biologically-active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral

diseases and manage their symptoms” [3]. As stated in the definition, FF are able to create health benefits by affecting biomarkers of disease such that they remain at low levels or are decreased, reducing the risk of disease. The reason that FF are able to affect biomarkers is because they are composed of bioactive compounds (BC) which are the “primary and secondary metabolites of nutritive and non-nutritive natural components that generate health benefits by preventing or managing chronic disease or its symptoms” [3-4]. These BC are the properties of FF that make them functional.

Given that functional food products (FFP) are meant to promote the health of consumers, ensuring their safety and efficacy is an important step prior to bringing them to the market. For that reason, the FFC has proposed a 16-step process to develop FFP and bring them to the market [3]. Previous articles have discussed the components of each step and how they are useful for the regulation and classification of FFP [3,5]. As part of this process, the FFC proposed that a specific goal be set in place for the FFP and determine which BC will be able to accomplish this goal [3]. Following this goal, the appropriate dosage at which the BC can create health promoting effects and be consumed safely must be found [3,6]. As previously discussed, the dosage of BC is usually determined by conducting preclinical and clinical trials. However, we previously proposed that using the Quantum theory of functional food science (FFS) can be used to establish dosage of BC by finding the critical amount of a BC needed to create a chain reaction that results in the claimed health benefits [6]. The Quantum theory of FFS helpful for determining the levels at which

a FFP is effective but is also useful in determining levels at which a FFP can be toxic, therefore establishing the range at which the FFP is both safe and effective [6].

As noted in our previous article, there are other factors that can influence the effectiveness and safety of a FFP, such as time, or *Tempus* in Latin. More research is needed to learn about the influence that time may have on the effectiveness of BC in FFP. Some FFPs may need to be consumed for longer time periods than others to create effects on biomarkers of disease. Other FFPs might only be effective for short periods of time and lose effectiveness after that time period and may even need to be used in cycles where it is consumed for some time (while it is effective) and not consumed for some time (while it is not effective). For this reason, not only is it important to learn more about the Quantum theory of functional food science to learn more about the safety of a FFP, but it is also important to understand the *Tempus* of functional food science to learn more about the efficacy of FFP. Due to its importance in creating a safe and effective product, in this paper it is proposed that a new step be included in the steps to bring a FFP to the market. As seen on table 1, this new step should occur after establishing the appropriate dosage of a BC in a FFP and should focus on the establishment of the appropriate consumption time of a BC, making the total process 17 steps. The time of consumption should be modified for different doses and populations, and eventually the results should be taken into consideration by doctors in order to finalize the appropriate dose and time of consumption for the FFP for an individual patient.

Table 1. Steps to develop FFP and bring them to the market as proposed by the FFC. This table was modified from the articles from references 3,5.

Step Number	Description of Steps to create FF Products
1	Establishes a goal of the functional food product,
2	Determines relevant bioactive compound(s),
3	Establishes the appropriate dosage of bioactive compound(s),
4	Establishes the appropriate time of consumption of bioactive compound(s),
5	Determines the specific pathway and mechanism of action,
6	Establishes relevant biomarker(s),
7	Chooses an appropriate food vehicle for bioactive compound(s),
8	Provides preclinical studies one efficacy and safety,
9	Provides clinical trials for dosage, time of consumption, efficacy, and safety,
10	Creates a special label that informs the consumers of the most effective way to consume the product,
11	Publications are submitted to peer-reviewed journals, preferably in open access,
12	Educates the general public,
13	Sends information to credible governmental agencies, such as the FDA, for approval,
14	Official establishment of the accredited functional food product,
15	Release the functional food product to the market. (Receive the basic category (level C)),
16	Provides epidemiological studies. (Reapply for the approval for a new category (level B)),
17	Provides after market research. (Reapply for the approval for a new category (level A)).

RETRIEVAL OF PUBLISHED STUDIES:

Articles for this review were found through the Functional Food Center website and Google Scholar. Multiple articles were viewed and screened, however not all were selected for this article. This is because the information in those articles were not deemed relevant to the topic of this review. In total, only 36 papers from the search were used for this article because they had relevant information. It is worth noting that not all of the information from the 36 articles was used for this review, as not all the information in the articles were relevant. Keywords used to find the references included terminology relating to bioactive compounds, functional food, dosage, chronic disease prevalence in the United States, quantum theory of functional food sciences,

allometric scaling, squalene, tempus theory of functional food science, and therapeutic time range.

QUANTUM THEORY OF FUNCTIONAL FOOD SCIENCE

Determining the appropriate dose of consumption of any substance is an important step for ensuring that it is able to produce the desired effects on the consumer while being safe. In medicine, a therapeutic time range is established for a drug which is the dosage of a drug that will create the desired effect on the patient [9]. As we have learned throughout the years, food products like medications are able to produce health promoting effects on consumers. However, it is also possible that too much consumption of foods and their BC can create toxic effects, which is why upper tolerable limits (UL),

(the maximum amount of a nutrient a person can consume without experiencing adverse effects) have been established for many micronutrients [10]. Similar to medicines, FFPs go through preclinical and clinical trials in which animal and human subjects are used to determine the amount of BC that is safe to consume and effective in reducing biomarkers of disease [3,6]. Although using animal subjects allows researchers to understand complex organisms better without having to use human subjects, it is not clear what the correct way to convert the dose from an animal subject to a human subject should be, which could lead to inappropriate amounts of a BC being used on human subjects [7]. There are different methods that have been used to make these conversions, including allometric scaling which, if used correctly, can effectively convert the appropriate dosage from animals to humans that should be used [8]. This technique is based on correlations between species that have similar characteristics and uses metabolic rates and body size to predict the appropriate dose for humans [8].

As previously discussed [6], Quantum theory describes energy at atomic and subatomic levels. The Quantum theory of functional food science describes the critical mass of a BC at which it is able to create chain reactions at a constant rate, which lead to changes in the body that are beneficial for health [6]. Quantum theory of FFS establishes the range of the dosage at which a BC is effective in promoting health by preventing or managing symptoms of disease. This has been demonstrated previously in an experimental study conducted on diabetic patients, in which in the course of 84 days patients were given different doses of squalene, which is a BC belonging to the triterpene class [11].

Squalene is a 30-carbon isoprenoid that is found in high amounts in Amaranth oil, with 100 grams of amaranth oil counting around six grams of squalene [12-13]. Previous studies have shown that the use of squalene could improve lipid profiles, [15-19] and proteinuria [20], as well as exhibiting antioxidant and anti-cancer properties [12]. In the studies conducted by Dr. Martirosyan and his co-authors, participants were divided into five groups including healthy controls, diabetic receiving 0 mg of squalene a day, diabetics receiving 200 mg of squalene a day, diabetics receiving 400 mg of squalene a day, or diabetics receiving 600 mg of squalene a day [11]. After 84 days, parameters of proteinuria including biomarkers from serum samples were analyzed [11]. It was determined that consuming squalene at doses of 400 mg - 600 mg a day was able to create the most significant improvements in some parameters of proteinuria [11]. Although at a dose of 400 mg a day squalene was able to effectively alter biomarkers and parameters of proteinuria in diabetic patients, when given a dose of 600 mg a day, patients saw better results [11]. This means that 400 mg of squalene was sufficient to create chain reactions that improved health outcomes, but those chain reactions occur more effectively at a dose of 600 mg a day. Using the Quantum theory of FFS, this study was able to find the range of dosage of the BC in which researchers could observe changes in parameters related to proteinuria. However, research in this area needs to be continued to see if the range of dose (400 mg - 600 mg a day) is accurate, or if this range is possibly broader with higher doses above 600 mg being equally or more effective in treating proteinuria in diabetic patients without creating adverse effects.

The methodology of the squalene study on proteinuria was repeated on a different group of diabetic patients to see if consumption of squalene would have an effect on lipid profiles and oxidative biomarkers of diabetic patients, and if so at what range these effects would occur [14]. Participants were once again separated into one of five groups, similar to the previous study. Every 14 days, samples were taken from participants, and after 84 days the parameters were analyzed [14]. The results showed that at doses of 200 mg – 600 mg a day, squalene improved high density lipoprotein cholesterol (HDL) levels and decreased low density lipoprotein cholesterol (LDL), cholesterol, and triglyceride levels, with the most improvement at dosages of 600 mg a day [14]. Interestingly, the effects of different dosages seemed to be time dependent, which will be discussed in this article. This study was able to show that supplementation with squalene was able to effectively improve oxidative and lipid profiles in diabetic patients, but the effectiveness of different doses was observed at different times (days) of supplementation. Results of this study suggest that not only is the Quantum theory of FFS important for bringing a safe and effective FFP to the market, but so is the Tempus theory of functional food science, which is discussed later in this article.

Not only is this theory useful for establishing the range of amounts at which a BC may be effective and create the claimed effects on health, but it can also be used to determine the amounts of a BC that are safe to consume. Although a food product may have beneficial effects, it could also become toxic for consumers at a certain point. Quantum theory of FFS can also be useful to determine the amount above the critical mass at which

a BC can become toxic and create adverse effects, making it unsafe for consumers [6]. For example, the BC vitamin C is the component of citrus fruits that brings on health benefits to consumers by acting as an antioxidant [21]. Researchers have found that at doses of 90 mg a day for men and 75 mg a day for women, vitamin C is able to effectively create chain reactions in one's body that promote health and prevent diseases [21]. Doses below that amount are not considered effective in maintaining and promoting health outcomes. On the other hand, although vitamin C intake is important for preventing scurvy and degenerative diseases and has antioxidant properties that reduce oxidative damage on DNA and helps maintain iron levels, too much consumption of vitamin C can be detrimental to health [21]. Researchers consider intake of doses above 2 g a day of vitamin C to be toxic as they can cause adverse effects [21]. This means that doses of 90 mg - 2 g a day for men and 75 mg - 2 g a day for women is considered the recommended amount that should be consumed. However, for people who have diseases like scurvy, cancer, or COVID-19, it might be best to consume a different amount than what is recommended for healthy individuals. This is because the recommended amount may not be enough to produce changes in biomarkers. In this case, patients may want to consider consuming the therapeutic range, or the amount needed to see significant effects on biomarkers of disease, rather than the recommended daily intake. For vitamin C, consumption in amounts of 300 mg -1000 mg a day can help improve symptoms [21]. Doses below this range may not be enough to create chain reactions that cause effects on health, while doses above this range might create accelerated chain

reactions that lead to toxicity and adverse effects. Although there are concerns regarding the safety of high dose supplementation of vitamin C, studies conducted on COVID-19 patients showed that high dose supplementation improved symptoms and reduced inflammation [22]. Although short term high dose supplementation of vitamin C can be helpful in improving symptoms and health of some patients, it may not be appropriate for all patients so doctors should frequently look at blood tests to ensure the treatment is not causing toxicity or increasing the risk of hypoglycemia [22]. Doctors might also consider other options for patients with renal impairment or glucose-6-phosphate dehydrogenase deficiency [22].

TEMPUS THEORY OF FUNCTIONAL FOOD SCIENCE

As seen above, finding the appropriate range of dosage is critical for determining the critical amount of a BC that should be present in a FFP in order for it to be effective and produce the health benefits that are being claimed. Not only is it important to create a product that is effective, but it is also important for ensuring that the FFP is safe for consumption and will be able to produce health benefits rather than adverse effects. Although the use of Quantum theory of functional food science to establish the appropriate dosage is an important step in bringing an FFP to the market, it is also important to consider how time may influence the effectiveness of an FFP. For this reason, both the Quantum theory of functional food science and Tempus theory of functional food science should be considered when creating a FFP.

Throughout the years, researchers have conducted multiple studies on BC to learn more about the effects

that they have on health and parameters of disease. Multiple studies that have been conducted have focused on identifying the BC and the foods they are present in, the effect that they have on people, and the mechanism by which they produce the effect [23]. This can be done by extracting the BC in question and conducting preclinical, including in vitro and in vivo studies, and clinical trials [23]. Not only do these studies determine the safety and efficacy of consuming a BC by establishing the appropriate dose of consumption, but they are also able to do so by establishing the appropriate time of consumption. Time course studies are able to provide information about how time influences the effectiveness of a BC by observing the amount of time it takes for it to be effective and how long these effects last [23]. More course studies are needed to learn about how long it takes for different BC to create chain reactions that can promote health or manage symptoms of different diseases. Furthermore, more time course studies should be conducted to examine how long the effects created from consuming the BC last.

While the Quantum theory of FFS looks at the critical amount needed to create a chain reaction, Tempus theory of FFS looks at the amount of time that it takes for a BC to be effective. The amount of time may vary with the type of BC as well as the dosage used. It may take consuming the BC for days, months, or years to see a reduction in biomarkers of disease, symptoms, or health benefits. Consuming a certain dosage of a BC one time or for very short time periods may not be enough for the chain reactions that are induced to create changes in health or biomarkers of disease. It is possible that for a BC to be effective in promoting health and treating or

managing disease symptoms, consuming the correct dosage may not be enough. Consuming the correct dosage for the correct amount of time may also be needed in order to receive the most benefits from the FFP. The dosage and time of consumption could be modified for different diseases and populations. It could also be modified through a more personal approach to ensure that each individual patient is consuming the most appropriate dose for the most appropriate time depending on their age, gender, and disease status, among other factors. The BC may need to be consumed for enough time such that enough of it accumulates in the body causing enough chain reactions to occur for long enough to see changes in health outcomes.

The studies discussed in the previous section are a great example of Quantum and Tempus theory of FFS in practice. Dr. Martirosyan and his co-workers conveyed the use of both theories to determine the critical amount at which the BC squalene could improve parameters of disease in diabetic patients as well as how time of consumption could affect what that critical amount was. For example, the critical amount in short term consumption was a larger dose of the BC, while the critical amount in long term consumption was a lower dose [11,14, 24-25]. Furthermore, the studies discussed in this paper were led in part by Dr. Danik Martirosyan, who is a co-author of this paper. Because of this, this article will discuss how Quantum and Tempus theory of FFS were used for the BC squalene in diabetic patients.

Quantum and Tempus theories of functional food science in practice: Previous research on the BC squalene

has shown the importance of Quantum theory in FFS, as mentioned above. However, the same research has also shown the importance of Tempus theory of FFS. While the results of both studies discussed earlier in this paper showed that at a range of 400 mg - 600 mg, supplementation of squalene was able to effectively reduce parameters of proteinuria and oxidation as well as lipid profiles, they also showed that the effects created by different doses were time dependent [11,14]. As seen in Figure 1, supplementation had a dose and time dependent relationship with levels of proteinuria with supplementation of larger doses creating larger effects in less time [11]. For parameters of proteinuria, doses of 600 mg began to see improvements on day 28 with the most improvement seen on day 84, suggesting that the appropriate range of time for consuming squalene at 600 mg a day to improve proteinuria levels is 28 - 84 days [11]. However, more research is needed to see if the range is appropriate as it could possibly be a wider range. A similar trend was observed with the two other doses where at day 28 they saw decreased proteinuria levels; however larger doses saw a larger decrease in proteinuria levels [11]. On day 28, diabetics consuming 600 mg a day of squalene had proteinuria levels of 16.95 mg/dl [11]. By day 56, consumers of 400 mg a day were able to reach similar levels of 16.03 mg/dl [11]. Results suggest that while it took 28 days to reduce levels of proteinuria to under 17 mg/dl for supplementation of squalene at 600 mg a day, it took 56 days for doses of 400 mg a day.

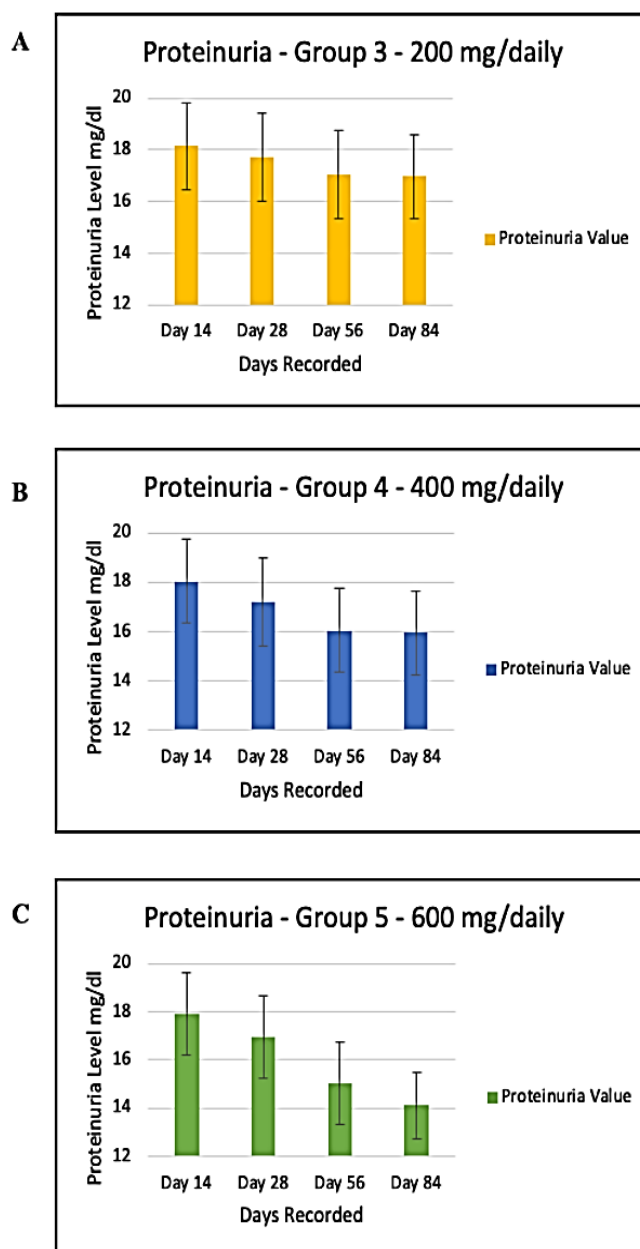


Figure 1 (A, B, C). Proteinuria levels in group 3 (200 mg of squalene a day), group 4 (400 mg of squalene a day), and group 5 (600 mg of squalene a day) over the course of 84 days [11].

Although the results are not as clear as for the effects of squalene on proteinuria, squalene also seems to have a time dependent effect on lipid profiles. As seen in figure 2A for doses of 600 mg, on days 28 - 56 HDL levels saw the most improvement, however consuming it for less than 56 days would not provide the consumer with optimal results [14]. Similarly, doses of 400 mg begin to create changes on HDL levels on day 28, but they take at least 56 days to produce the same effects on HDL as consuming a daily dose of 600 mg for 28 - 56 days [14].

As for doses of 200 mg a day, consumers would need to ingest squalene for at least 84 days to see similar effects of taking larger doses for less time [14]. Interestingly, for those consuming 600 mg and 400 mg of squalene a day, at day 28 they saw reductions in LDL with the most reduction being seen on day 56, however there was an increase in LDL levels at day 84 as seen in figure 2B [14]. This suggests that doses of 600 mg a day of squalene are the safest and most effective in improving lipid profiles if taken for 28 - 56 days. Similarly, doses of 200 mg a day

saw the most reductions in LDL at day 56, however patients consuming this dosage saw an increase in LDL levels in the first 28 days [14]. This suggests that consuming 200 mg of squalene a day for 56 days may create the most effective results for LDL levels at this dosage. It should be noted that although all doses saw

the most reduction in LDL at 56 days, doses of 600 mg a day saw the most reduction followed by doses of 400 mg [14]. More research should be conducted to confirm the exact time range of different doses to establish the range of time at which different doses are most effective in improving lipid profiles.

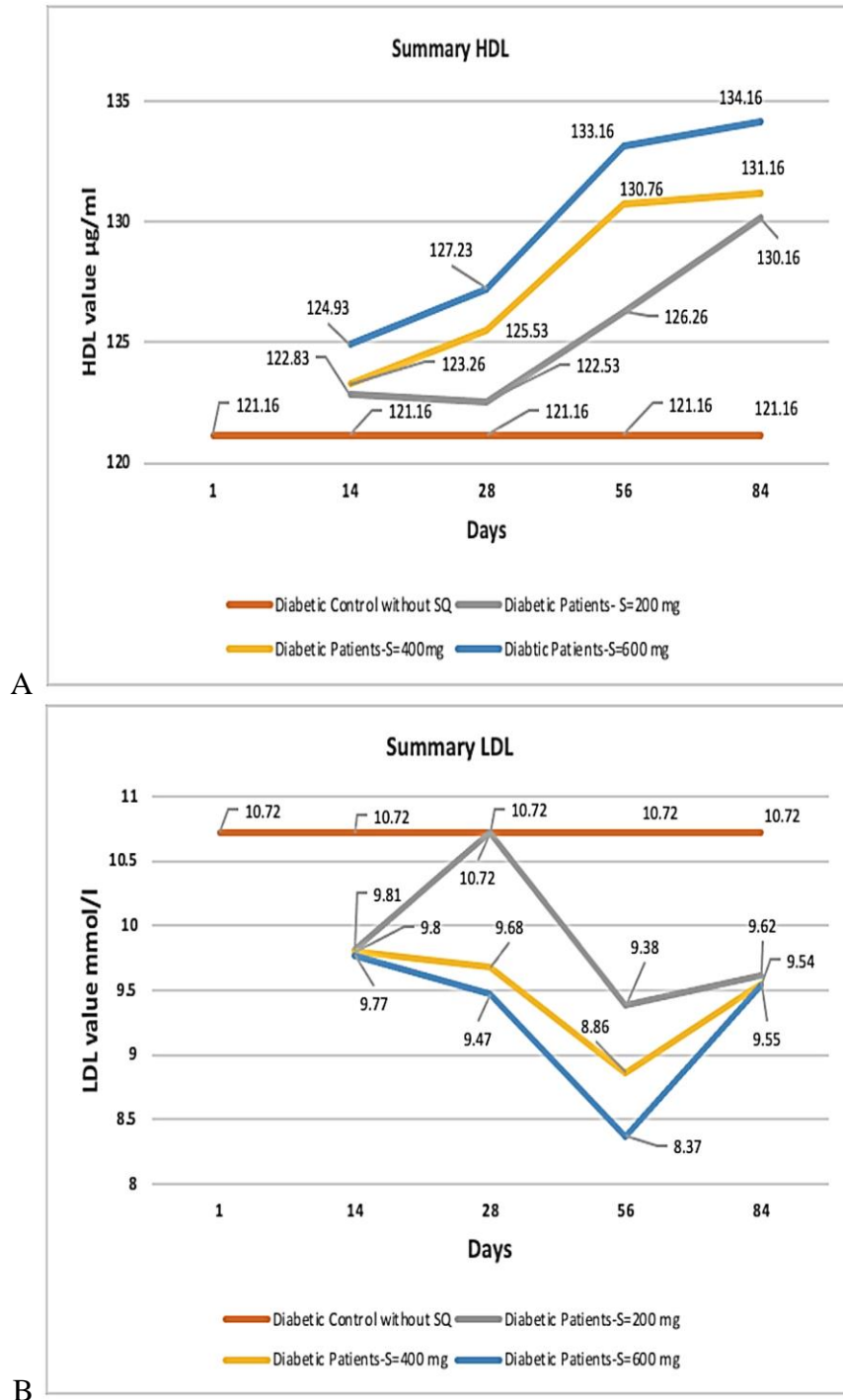


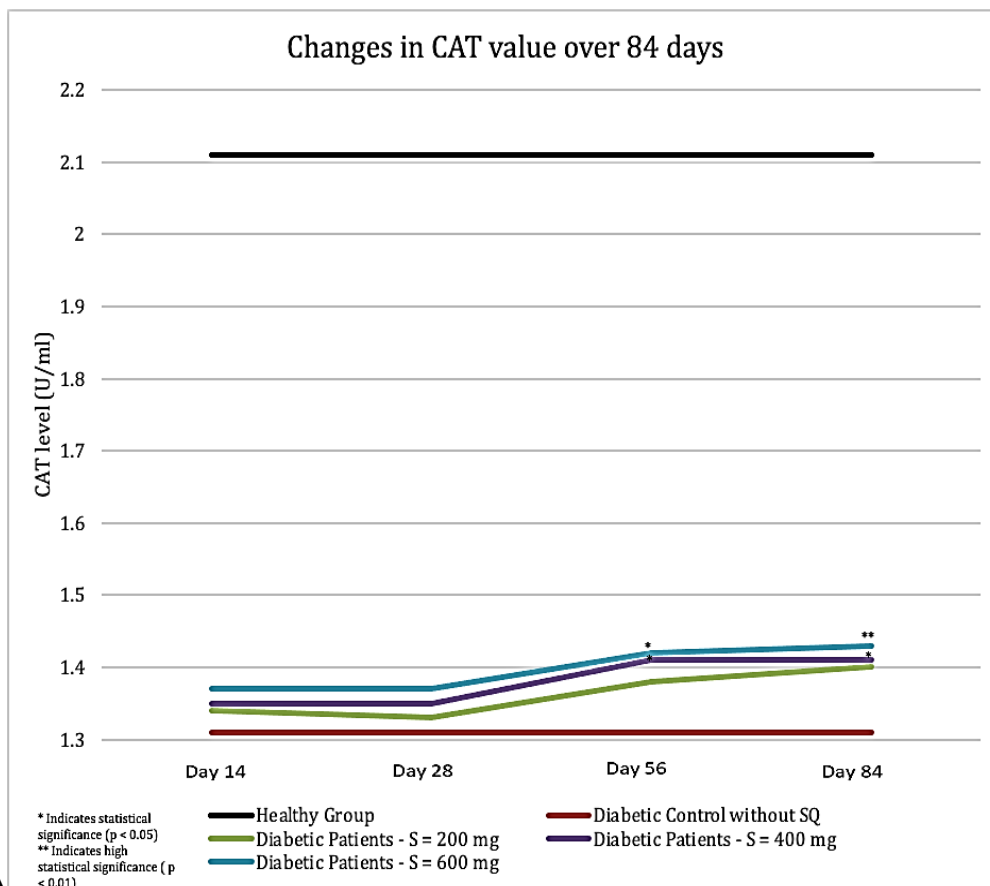
Figure 2 (A and B). Effects of consumption of different doses of squalene on HDL and LDL levels in diabetic patients over the course of 84 days [This image was modified from images from reference 14].

As seen in Table 2, consumption of squalene also had effects on inflammatory factors and immunoglobulins in a time and dose dependent manner. The study focusing on inflammatory factors and immunoglobulins that was referenced in Table 2 looked at the effects of different dosages of squalene across 84 days on inflammatory biomarkers of diabetic patients including interleukin-1 alpha (IL-1 α), interleukin-1 beta (IL-1 β), interleukin-4 (IL-4), immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM) [24]. In the study, levels of IL-1 α and IL-4 saw a significant decrease by the 14th day in participants consuming 600 mg of squalene [24]. Similar to IL-1 β and IgA, the different doses of IL-1 α saw the most reductions on days 56-84 compared to participants not consuming squalene [24]. Levels of IgG had fluctuations throughout the trial, but all groups saw a decrease by the end of the trial, unlike for IgM which increased in all groups [24]. The results of this study showed that consumption at any dosage of squalene can lead to improvements in some inflammatory and immunoglobulin parameters, however these improvements differ according to dosage and time of consumption. As expected, the largest dose of 600 mg of squalene a day produced the most reduction in these parameters followed by 400 mg and 200 mg of squalene a day [24]. Although the time range is similar for the different doses tested, most improvement was seen with intake of larger doses. However, more research is needed to confirm that the time range suggested by the results of the study is appropriate for improving inflammatory and immunoglobulin parameters in diabetic patients.

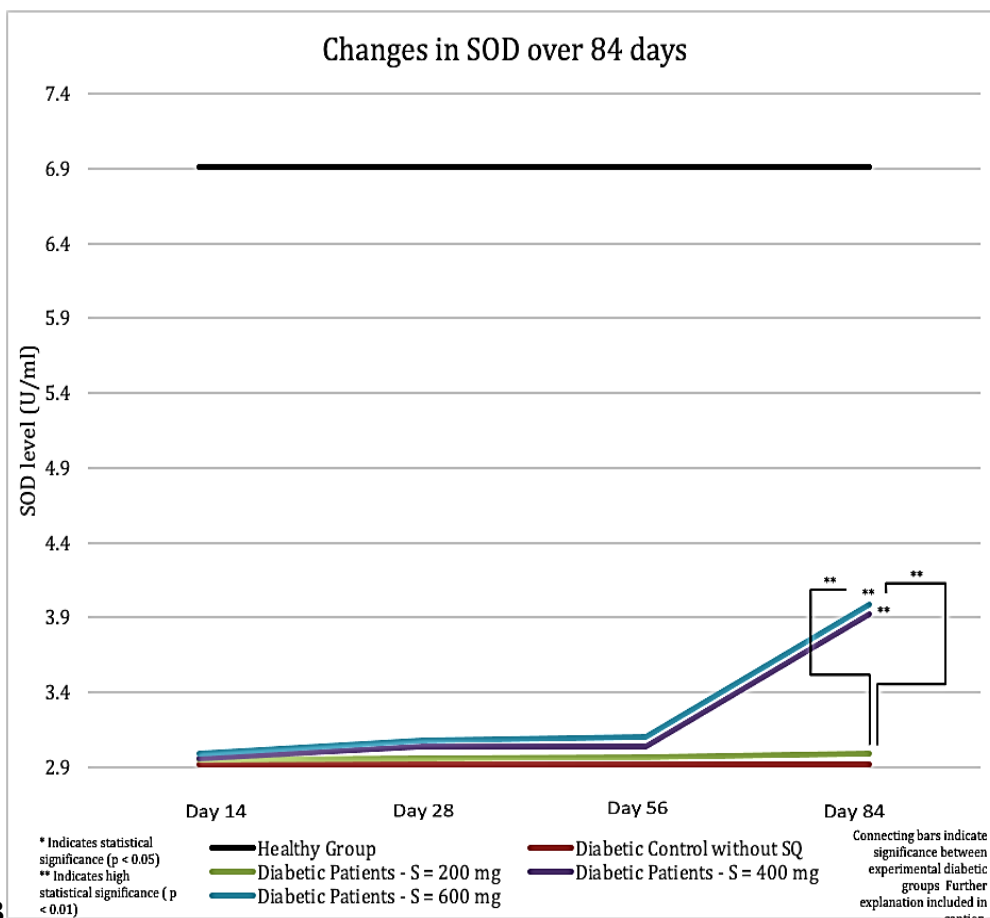
Lastly, Dr. Martirosyan and his co-workers looked at how squalene consumption at different doses across 84 days would affect levels of antioxidant enzymes and compared them to levels of healthy participants. As seen in Figure 3A, levels of catalase (CAT) saw significant improvements on days 28-56 [25]. Interestingly, levels of

superoxide dismutase (SOD) remained unchanged until day 56, however this was only true for participants consuming over 400 mg of squalene a day [25]. More research is needed to understand the appropriate range of time of consumption for improving levels of SOD, however as suggested by figure 3B, it takes at least 56 days to see an effect on SOD levels at dosages of 400 mg - 600 mg of squalene a day [25]. As for levels of glutathione peroxidase (GPx) consumption of squalene increased GPx levels from days 14-28, however this was only significant for dosages of 600 mg a day for 28 days as seen on figure 3C [25]. Although the levels of antioxidant enzymes saw improvement at certain points in time, the levels did not reach the same or similar levels to that of healthy participants for any of the parameters or dosages [25]. For that reason, future research should provide supplementation of squalene for more than 84 days to see how long the different dosages of squalene should be consumed for diabetic patients to have similar levels of antioxidant enzymes as healthy participants. study also looked at the effects of squalene on levels of free radicals, which were also compared to those of healthy participants.

As seen in Figure 4A and 4B, consumption of squalene decreased levels of hydrogen peroxide (H₂O₂) and reactive oxygen species (ROS) from days 14-84 for all dosages, with the largest decrease in participants consuming 600 mg [25]. Similarly, levels of nitric oxide (NO) decreased with consumption of squalene [25]. As seen on Figure 4C, participants consuming 600 mg a day of squalene saw a highly significant decrease in NO from days 14-84, those consuming 400 mg a day on days 28-84, and those consuming 200 mg a day on days 56-84 [25]. More research is needed to find the exact time range at which different doses of squalene improve levels of free radicals.



A



B

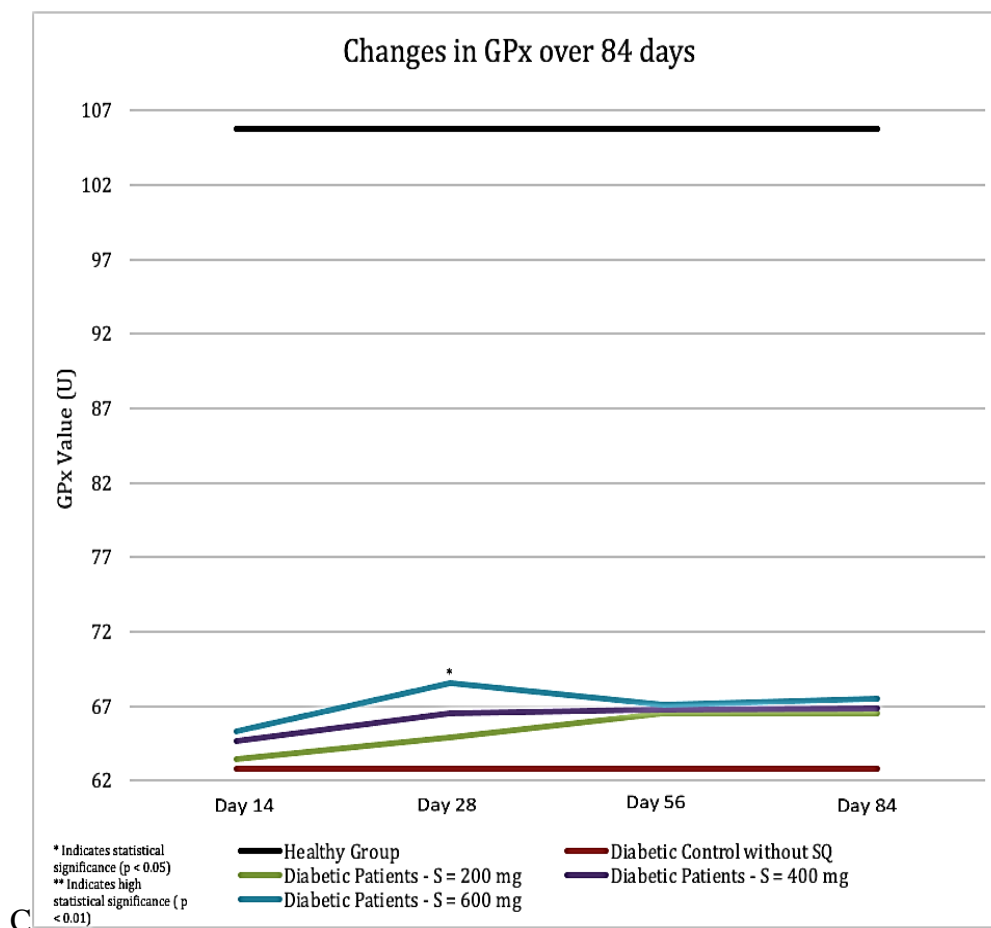
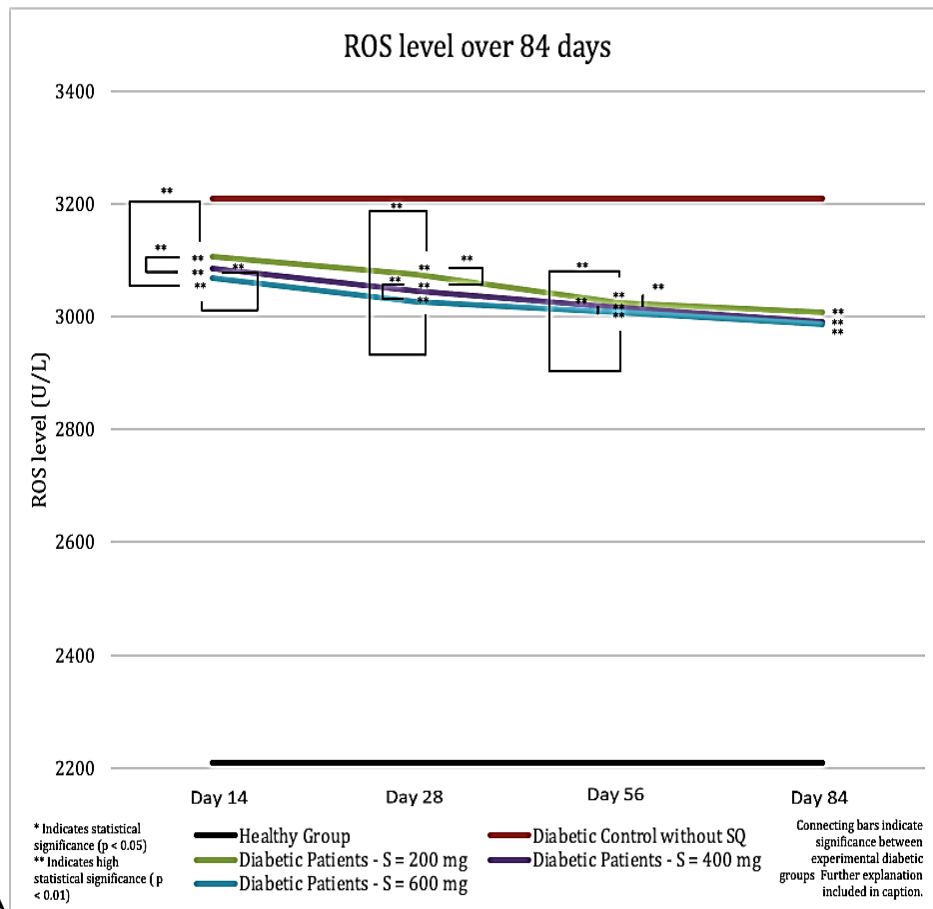


Figure 3 (A, B, and C). Changes in levels of antioxidant enzymes CAT, SOD, and GPx in healthy patients and diabetic patients consuming different daily doses of squalene (0 mg, 200 mg, 400 mg, and 600 mg) over the course of 84 days [25]

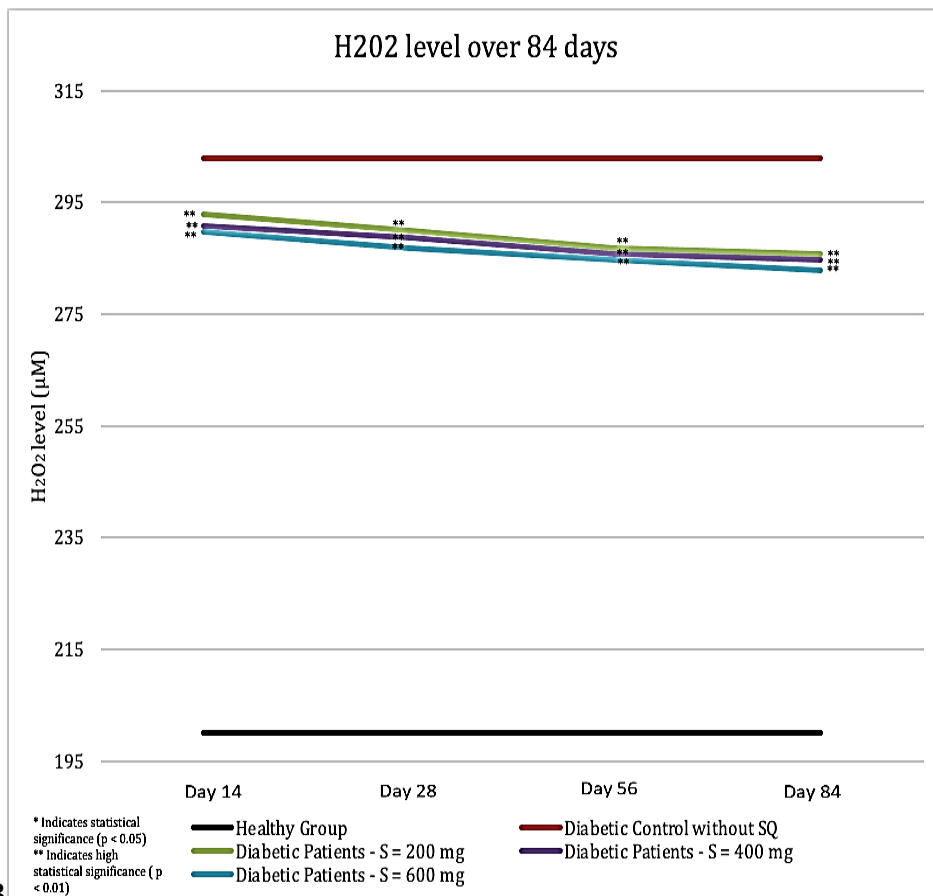
Similar to levels of antioxidant enzymes, although levels of free radicals saw improvement at certain points in time, they did not reach the same or similar levels to that of healthy participants for any of the parameters or dosages [25]. For that reason, future research should provide supplementation of squalene for more than 84 days to see how long the different dosages of squalene should be consumed for diabetic patients to have similar levels of free radicals as healthy participants.

The study also looked at the effects of squalene on levels of free radicals, which were also compared to those of healthy participants. As seen in Figure 4A and 4B, consumption of squalene decreased levels of hydrogen peroxide (H2O2) and reactive oxygen species (ROS) from days 14-84 for all dosages, with the largest decrease in participants consuming 600 mg [25]. Similarly, levels of nitric oxide (NO) decreased with consumption of

squalene [25]. As seen on Figure 4C, participants consuming 600 mg a day of squalene saw a highly significant decrease in NO from days 14-84, those consuming 400 mg a day on days 28-84, and those consuming 200 mg a day on days 56-84 [25]. More research is needed to find the exact time range at which different doses of squalene improve levels of free radicals. Similar to levels of antioxidant enzymes, although levels of free radicals saw improvement at certain points in time, they did not reach the same or similar levels to that of healthy participants for any of the parameters or dosages [25]. For that reason, future research should provide supplementation of squalene for more than 84 days to see how long the different dosages of squalene should be consumed for diabetic patients to have similar levels of free radicals as healthy participants.



A



B

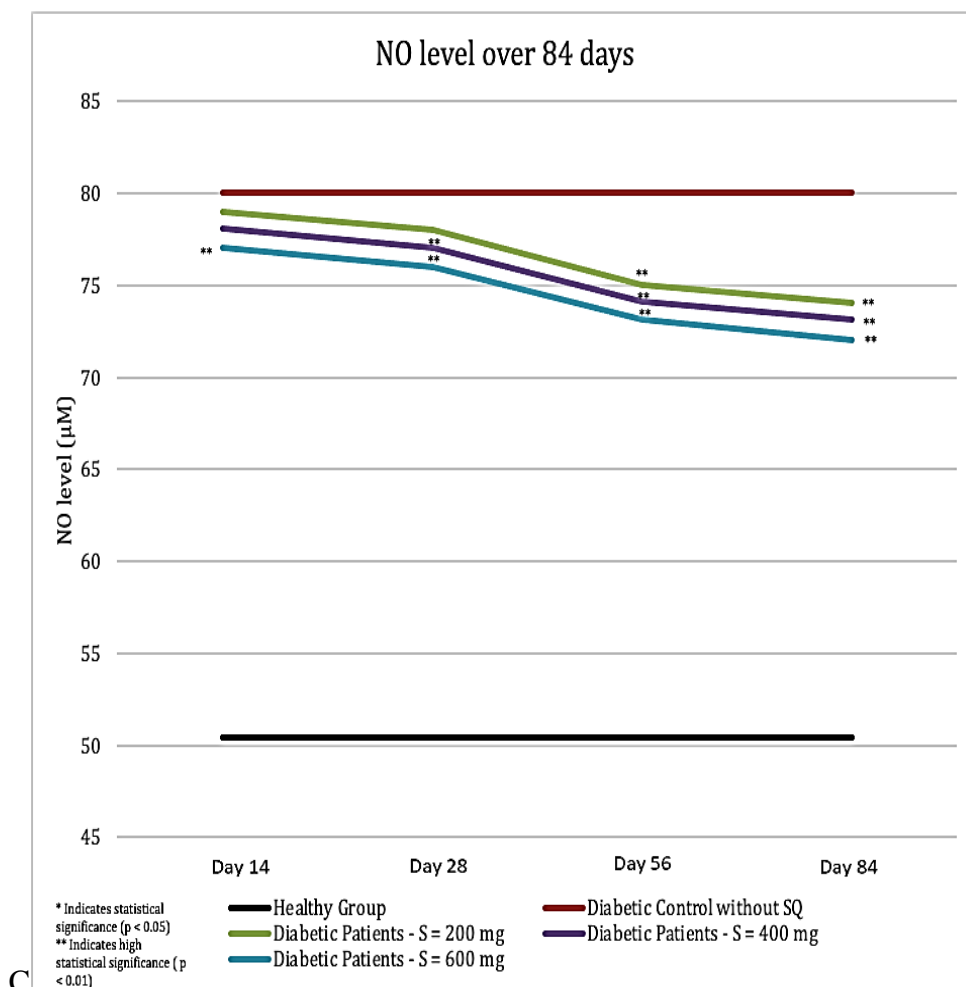


Figure 4 (A, B, and C). Changes in levels of free radicals H2O2, ROS, and NO in healthy patients and diabetic patients consuming different daily doses of squalene (0 mg, 200 mg, 400 mg, and 600 mg) over the course of 84 days [25].

As seen in the squalene experiments, the appropriate dosage and time of consumption for a BC will be a range of dose and time. When consuming a BC the claimed health effects do not occur immediately, but they occur after a certain amount of time. The results of the experiments of squalene consumption on diabetic patients suggest that at some point in time enough BC accumulates in the body and enough chain reactions occur that changes in health and biomarkers of disease can be seen. Of importance is the total consumption of squalene of 5600 mg, 11200 mg, 16800 mg, and 33600

mg, as seen in Table 2 which was modified from the four articles looking at consumption of squalene in diabetic patients. Total consumption of squalene at these amounts shows improvement of parameters of disease, however the amount of time that it takes to see these improvements differs based on the amount that was consumed daily. As seen in Table 2, when a total amount of 5600 mg of squalene is consumed levels of immunoglobulins, glucose, lipid profiles, inflammatory biomarkers, and other parameters reach similar amounts for diabetic patients consuming 200 mg of squalene a day

and those consuming 400 mg of squalene a day. Although they reached similar levels, those consuming 400 mg of squalene a day reached those improved levels on day 14 while those consuming 200 mg of squalene a day reached the levels on day 28. At a total dose of 16800 mg of squalene, diabetic patients reached similar levels of the parameters measured for those consuming 200 mg of squalene a day and those consuming 600 mg of squalene a day, however those consuming higher doses saw improvements on day 28 while those consuming lower doses reached similar levels on day 84. Similarly, at a total dose of 33600 mg of squalene patients consuming 600 mg of squalene a day reached more improved levels in parameters on day 56 while those consuming 400 mg of squalene a day reached similar levels on day 84. Although most parameters of disease saw improvements in participants consuming different doses, when they consumed a total amount of the BC and it accumulated in the bodies of participants, the participants reached similar levels of the parameters measured. However, the time at which they saw these improvements differed, with consumption of larger daily doses of squalene reaching the levels sooner than those consuming smaller daily doses. This may be due to the fact that those consuming larger daily doses accumulated the total amount of squalene faster than those consuming smaller doses. It should be noted, however, that although the levels of the measured parameters reached similar

amounts between those consuming different daily dosages, none of the groups reached levels similar to that of healthy participants. For this reason, more research is needed with more time in order to get a better idea of the total amount of squalene that needs to be consumed for diabetic patients to reach similar levels of the measured parameters to that of healthy patients as well as how many days it would take for the groups consuming different dosages to reach these levels.

Understanding what the appropriate time range is for consumption of a BC can allow doctors to evaluate their options and pick the best one. For example, patients with more advanced diseases might benefit more from consuming higher doses of a BC for less time than consuming lower doses for longer periods. This is especially true for time sensitive cases because they need supplements and treatments that work fast. Depending on characteristics of the patients including age, gender, and disease status, doctors can choose the best option for their patients whether it be lower doses for more time or higher doses for less time. The safe and effective ranges of dosage and time are established by Quantum theory of FFS and Tempus theory of FFS, respectively. Although both of these methods look at safety of dosage and time of consumption, when considering the best option for individual patients it would be important to consider possible side effects that are not adverse that could occur with different dosage and time ranges.

Table 2. Health parameters of diabetic patients consuming different dosages of squalene across 84 days [This table was modified from tables found in articles from references 11,14, 24-25].

Parameters on day 14	MDA	ox-LDL	IL 1 α	IL 1 β	IL4	IgA	IgG	IgM	Glucose	Chol	TG	LDL	HDL	VLDL	CAT	SODM	Cystatin C	Total SQ(Mg)
Diabetic Patients - S=400 mg	3.6	20.1	906.8	420.9	153.9	42.54	4.52	10.13	395.93	190.03	140.4	9.8	123.3	40.2	1.4	2.97	14.8	5600
Parameters on day 28	MDA	ox-LDL	IL 1 α	IL 1 β	IL4	IgA	IgG	IgM	Glucose	Chol	TG	LDL	HDL	VLDL	CAT	SODM	Cystatin C	Total SQ (Mg)
Diabetic Patients - S=200 mg	3.6	19.72	923.43	433.93	150.9	43.02	4.5	10.12	396.3	189.03	140.03	9.9	122.53	39.8	1.34	2.97	14.8	5600
Diabetic Patients - S=400 mg	3.6	19.61	914.7	425.7	148.9	42.9	4.5	10.33	395.73	187.03	138.13	9.69	125.53	38.6	1.35	3.04	14.73	11200
Diabetic Patients - S=600 mg	3.54	19.14	903.23	417.5	142.9	42.34	4.51	10.74	395.6	181.03	136.2	9.5	127.23	37.44	1.4	3.1	14.72	16800
Parameters on day 56	MDA	ox-LDL	IL 1 α	IL 1 β	IL4	IgA	IgG	IgM	Glucose	Chol	TG	LDL	HDL	VLDL	CAT	SODM	Cystatin C	Total SQ (Mg)
Diabetic Patients - S=200 mg	3.5	19.44	883.8	406.9	145.9	40.44	4.6	10.24	396.03	185.4	134.4	9.4	126.3	38.4	1.4	2.97	14.8	11200
Diabetic Patients - S=600 mg	3.42	18.32	876.8	400.9	139.9	38.5	4.8	10.81	395.23	178.03	130.73	8.4	133.2	33.3	1.42	3.1	13.71	33600
Parameters on day 84	MDA	ox-LDL	IL 1 α	IL 1 β	IL4	IgA	IgG	IgM	Glucose	Chol	TG	LDL	HDL	VLDL	CAT	SODM	Cystatin C	Total SQ (Mg)
Diabetic Patients - S=200 mg	3.5	19.04	881.8	404.9	144.9	40.4	4.5	10.13	395.93	181.03	134.4	9.63	130.2	38.4	1.41	2.99	13.8	16800
Diabetic Patients - S=400 mg	3.44	18.81	879.8	402.9	142.9	39.41	4.47	10.19	395.57	180.23	133.4	9.6	131.2	37.41	1.42	3.93	13.8	33600

For example, a patient could be supplemented with 600 mg daily of a BC for 30 days to improve parameters of a disease and experience side effects of headaches and nausea, however when they are supplemented with 400 mg daily of a BC for 45 days, they do not experience any side effects and see significant improvements in parameters of a disease. In this sense, finalizing the appropriate dosage and time of consumption can also allow doctors to make an individual plan for consumption of a BC or FFP for a group or an individual patient.

LIMITATIONS

Although the studies discussed in this paper demonstrated the use of Quantum and Tempus theories in FFS, there are some limitations. As mentioned above, the studies used a limited range of dosages and were relatively short term (84 days). More studies with more varieties of dosage is needed to conclude that that range of time is correct. It is possible that to improve levels of proteinuria consumption of squalene at 600 mg a day could have an appropriate time range of consumption broader than 28 - 84 days, as it may take more than 84 days of consumption for the effect to decrease and therefore not be as effective. It is important to consider that at a certain point of time a dosage may not be as effective even if the dose is increased. This was seen in patients consuming 600 mg and 400 mg of squalene a day, who at day 56 saw reductions in LDL and at day 84 saw increases in LDL levels [14]. In this case doctors should also consider their best options and see what dose and time of consumption is best for their patients health. For this reason, it is important to find not just the range of dose at which a BC is safe and effective, but also the range of time, which could be found using Quantum theory of FFS and Tempus theory of FFS, respectively.

Another limitation is that only one example, that of squalene on diabetic patients, was discussed to show the relationship between dosage, time, and effectiveness of

BC. Although, Quantum and Tempus theories of FFS can still be applied to other BC and in other populations. It is possible that the range of dosage and time of consumption at which a BC is effective may differ in individuals that are healthy or in individuals with different diseases. For example, in the case of squalene, in a person with diabetes squalene may begin to improve lipid profiles at doses of 600 mg in 28 days, but in someone with cardiovascular disease the same amount of improvements may be seen with consumption of squalene at a different dosage or time of consumption. This concept is conveyed with the FFP Fibersol[®]-2 in which different doses are recommended for individuals wanting to improve different parameters [28]. Fibersol[®]-2, which is a FFP that has been approved as a standardized FOSHU [26]. FOSHU, or Foods for Specialized Health Uses, is used by the Japanese Ministry of Health as a way to regulate FF by being tested to assess safety and efficacy of the ingredients, dosage, and time of consumption of the product [27]. For improvements in intestinal irregularity, it is suggested that consumers consume 3-8 g of Fibersol[®]-2 however, for improvements in parameters of blood glucose it is suggested that 4-6g be consumed of Fibersol[®]-2 [28]. Several studies have been conducted to determine the appropriate dosage of the product for different functions. Fasting et. al suggested consumption of 15g/meal could improve gut microbiome health [29], while Burns et. al suggested consumption of 25g/meal was most beneficial for gut microbiome health [30]. Similarly for satiety Ye et. al suggested consumption of 10g/meal would be best [31], while Fernandez-Raudales et. al suggested 11g/meal was most effective for satiety [32]. Future research should use Quantum and Tempus theory of FFS to determine the appropriate time range for consumption of different BCs and FFP, including squalene and Fibersol[®]-2, in different populations to ensure safe and effective consumption of FFP.

Future research should also consider how the type of BC may affect dosage and timing as well. For example, vitamins and minerals exhibit genomic and nongenomic effects that can maintain and/or improve health [33]. However, some vitamins may be present in foods and in our bodies in different forms. For example, vitamin A can be found in various forms in foods including retinols, retinyl esters, and carotenoids [34-35]. Similarly, vitamin D can be found as either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in foods, with cholecalciferol being more potent [35]. In a study conducted by Hammami and Yusuf where supplementation of either vitamin D2 or vitamin D3 were given to participants under different instructions for time of consumption (daily, bi-weekly, or monthly) to see which type of vitamin D and timing of consumption would best increase serum 25(OH)D levels [36]. Interestingly, the study found that supplementation of vitamin D as ergocalciferol created better results when provided on a daily basis in the 20 weeks of supplementation, and supplementation of cholecalciferol was more effective when given biweekly [36]. Not only should dosage, time of consumption, and characteristics of the target population be considered, but also the different forms available in food products of the BC and how that may affect bioavailability and effectiveness depending on mode of delivery, dosage, and time of consumption.

CONCLUSION

The Functional Food Center proposed 16 steps to bring a FFP to the market, with the third step being that the appropriate dosage of a BC should be established. In this step, the use of Quantum theory of FFS could be used to establish the critical amount of a BC at which it can create chain reactions in the body that lead to health promotion and/or treatment or management of symptoms of disease. In this step, the dosage at which a BC is safe and effective is determined. In this paper it was proposed

that an additional step in which time of consumption is established be included in that process, which should be implemented after establishing the dosage making the total steps 17. In this new step, the appropriate time of consumption should be established using the Tempus theory of FFS. Tempus theory of FFS could be used to determine the appropriate time of consumption of the product needed to see improvements in health. This step is important because like dosage, time of consumption can influence the effectiveness of a BC. For example, consuming a FFP for a week may not lead to changes in biomarkers of disease, however consuming a FFP for 14 weeks may improve them. Quantum and Tempus theory of FFS can also allow doctors to understand more about how dosage and time can influence the effects of a FFP and allow them to make the best choice and personalize treatment for their patients when recommending consumption of these products.

Dr. Danik Martirosyan, a co-author of this paper, along with his collaborators, conducted investigations on squalene consumption in diabetic patients and in doing so conveyed the use of Quantum and Tempus both in FFS theory and in practice. In this article we discussed a new methodology used to evaluate scientific data from clinical research on the effects of squalene on the different parameters of patients with type 2 diabetes. The results of the four studies discussed provided more information on how different doses of squalene affect biomarkers of disease and parameters of health in diabetic patients and how the changes are influenced not only by the amount of BC consumed but also the amount of time in which it is consumed. For that reason, it was concluded that finding the appropriate dosage of bioactive compounds as well as time of consumption is an important step in the process of development of functional food products. The results of the studies suggested that squalene was able to produce beneficial effects on the measured parameters in patients with type

2 diabetes. By using Quantum and Tempus theory of FFS we were able to conclude that in individuals with type 2 diabetes consuming squalene in amounts of 600 mg for 84 days may reduce LDL cholesterol, in amounts of 600 mg for 56 days may enhance HDL cholesterol, and in amounts of 600 mg for at least 84 days may reduce levels of proteinuria. By applying the use of Quantum and Tempus theory of FFS, future research should be conducted to find the exact dose and time range that squalene should be consumed for diabetic patients for the management of several parameters. Especially for the effects of squalene on proteinuria levels in diabetic patients since the positive effects of the BC continued even at the highest dose offered (600mg) and for the longest time of consumption investigated in the study (84 days). Future research on this parameter should consider higher doses and longer time periods. Similarly for SOD levels, the positive effects of squalene were only visible after 56 days in individuals consuming doses of 400 mg and 600 mg, suggesting that chain reactions began at around 56 days and continued to increase at 84 days and possibly thereafter. For this reason, we suggest that future studies continue to look at the parameters discussed but consider a wider range of doses and days of consumption.

Given that the only example discussed was that of squalene in diabetic patients, which is a limitation of this paper, more studies are needed to find the exact

dose and time range at which other BC are effective in different populations in order to further convey the use of Quantum and Tempus theory in research.

Abbreviations: FFC: functional food center, FF: functional foods, BC: bioactive compounds, FFP: functional food products, FFS: functional food science, UL: upper tolerable limits, IL-1 α : interleukin-1 alpha, IL-1 β : interleukin-1 beta, IL-4: interleukin-4, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol, GPx: glutathione peroxidase, NO: nitric oxide, ROS: reactive oxygen species, CAT: catalase, SOD: superoxide dismutase, H₂O₂: hydrogen peroxide

Conflicts of Interest: There are no conflicts of interest associated with this study.

Authors' Contribution: The original idea (The concept of quantum and tempus theory of functional food science) was conceived by DM and was discussed with SS. SS collected data and wrote the manuscript. DM advised, participated in writing, and editing manuscript.

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