Annals of Integrative Oncology

Review Article
Published 27 Apr, 2022

A Novel Theory of Classifying Disease with Potential for Diagnosis, Prophylaxis, and Therapeutic Approaches

Natalia Chaikovskaia[1], Natalya V Khmil[2] and Homer S Black[3]*

[1]*Scientific and Production Association Oxygen Ltd., Smolensk, Russia*

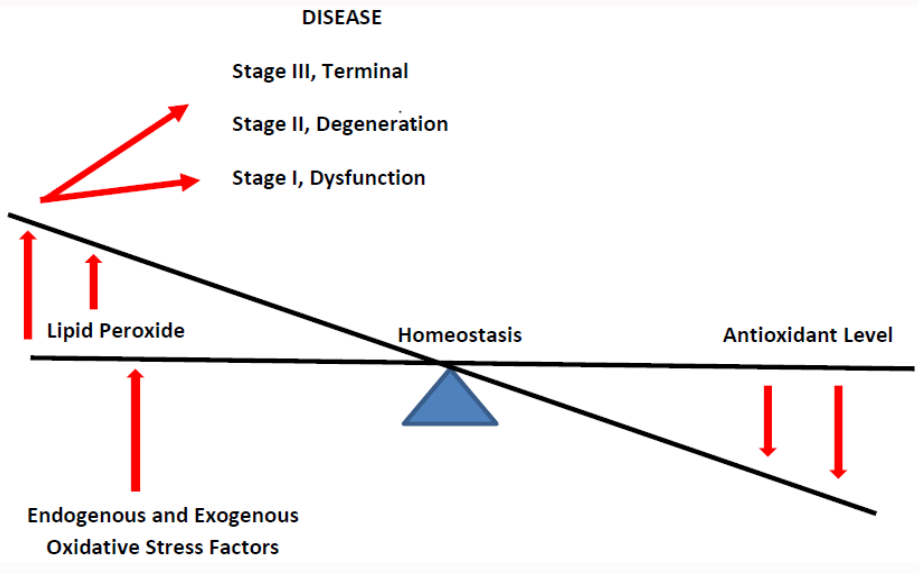
[2]*Inst. Theoretical and Experimental Biophysics RAS, Institutskaya str 3, Pushchino, Moscow region, 142290, Russia*

[3]*Baylor College of Medicine, Houston, Texas, USA*

Abstract

Early medical theory, appearing at different times and locales, proposed that good health was manifested in an equilibrium (homeostasis) of one's protective mechanism complex and offending stress agents. The protective complex includes the immune, biochemical, and other systems of the body. Stress factors may involve endogenous factors, e.g., steroid hormones, catecholamines, hypoxia, inflammation, etc.; exogenous factors, e.g., drugs, carcinogens, mutagens, allergens, and environmental agents; and anthropogenic loadings, e.g., smoking, excess drinking, etc. Under the influence of these stress factors, the defense mechanism(s) may be unable to neutralize induced changes in the internal organ environment and visible symptoms of "disease" begin to appear. Based upon the body's failure to restore the resulting imbalanced homeostasis, the overall health condition moves to an inflammatory stage and then to an incipient disease stage I, (dysfunction); followed by disease stages II (degeneration) and stage III (terminal). We propose that identification of these classes of disease can be determined by following lipid hydroperoxide/antioxidant homeostasis, in conjunction with classical clinical diagnosis. Further, measuring antioxidant status has significant diagnostic and treatment prognostic importance in defining the level of organism damage. Collective sera data for a range of disorders from small pelvis inflammation, pneumonia, stomach ulcer, duodenal ulcer, rheumatic diseases, severe bronchial asthma, and liver cirrhosis indicate a progressive decline in antioxidant status and an increase in lipid hydroperoxide level as the destructive disease processes progress. Although a broader data base must be accrued, this approach represents an exciting and important approach to determine disease development and potential means of intervention and therapy (Graphic Abstract).

Keywords: Lipid hydroperoxide; Antioxidant activity; Lipid peroxide/Antioxidant activity ratio; Disease stage; Homeostasis



Graphic Abstract:

OPEN ACCESS

Correspondence:
Natalia Chaikovskaia, Scientific and Production Association Oxygen Ltd., Smolensk, Russia,
E-mail: natalia_ch@inbox.ru

Received Date: *04 Apr 2022*
Accepted Date: *19 Apr 2022*
Published Date: *27 Apr 2022*

Citation:
Chaikovskaia N, Khmil NV, Black HS. A Novel Theory of Classifying Disease with Potential for Diagnosis, Prophylaxis, and Therapeutic Approaches. Ann Integr Oncol. 2022; 2(1): 1011.

Abbreviations

LHP: Lipid Hydroperoxide; AOA: Antioxidant Activity

Introduction

Among the early philosophic influences of Greek medical theory, that which came from the Pythagorean school of South Italy (Magna Graecia) provided some extraordinary vision regarding human health [1]. Alcmaeon of Croton was the main physician of that school and proposed that good health was the result of equilibrium between bodily forces and that disease resulted when these forces became imbalanced. This has been a guiding force of medicine throughout the World from the Hippocratic Medical writings of equilibrium of the humors; Empedocles' four elements; Galen's four temperaments; to the "yin" and "yang" of Chinese medicine. This underlying principle of imbalance remains today but as we have gained more knowledge of the complexity and intricacies of the human body we now must deal with a myriad of interacting systems. There is no unique model or understanding of the human body and how it functions in health and disease. Many current medical investigations are limited by cell or tissue culture models that often focus on a singular, specific aspect or dysfunction of disease.

Review of ancient medical knowledge, appearing at different times and locales indicate that much of this knowledge is still applicable. Certain regularity necessary for the healing process emerges from this knowledge today - namely the purification of the body from toxins. Generally, then, the problem of health *vs.* disease is dependent on whether there are enough resources in the organism for maintenance of natural defense (homoeostasis) throughout the organism's systems. This may be referred to as the protection mechanism complex and includes immune, reticuloendothelial, hormonal, sympathetic and parasympathetic, lymphatic and other systems. This natural complex is amazingly sophisticated and our knowledge remains incomplete. However, the overall purpose of this complex is self-protection of the organism *via* maintenance of homeostasis necessary to prevent imbalance and the resulting disease. Under normal conditions all of these defense mechanisms go unnoticed. However, under the influence of stress factors the defense mechanisms are unable to neutralize sudden changes in the internal organ environment and visible symptoms begin to appear from the organ site. Thus, the central theory of disease proposed by Alcmaeon (VI B.C.) remains valid today.

The main feature of the protection mechanism complex is to automatically produce response reactions in accord to the stress factor and to combat the developing disorder and restrict it to peripheral imbalanced expressions. The examples of these peripheral expressions such as fever, edema, convulsion, anxiety, depression, and generally any symptom that can appear in an organism under stress, is not the disease, per se, but a tool by which the organism tries to combat the disease. It is incumbent upon the scientific and medical communities to try to find not only any chemical, therapeutic, or biological substance that removes the symptoms caused by the pathogenic entity but most importantly to understand why the organism allows disease conditions to develop and then how to support the body's protective mechanisms that allow reversal of the disease progress.

It is to this end that a unique and rational approach to determine disease development and potential means of intervention has been proposed. The basis for this approach is based upon an understanding that a healthy human can activate and maintain protection systems and purify itself. In the case of persistent suppression of homeostatic systems, with lack of intoxication removal, the health condition moves to an incipient-disease stage followed by later stages of disease and cell and organ destruction. These changes can be followed by analyzing peroxide and antioxidant homeostasis parameters. It is herein proposed that identification of these disease classes can be determined by analyzing lipid hydroperoxide/antioxidant homeostasis. Together with classical clinical analysis, this approach constitutes a strong diagnostic tool to assess a patient's health status with potential for diagnoses, determining disease progress, and influence of therapeutic approaches.

Peroxide Homeostasis Theory

The importance of biological free radicals and their metabolism cannot be overemphasized. Under normal oxidative metabolism endogenous Reactive Free Radicals (ROS) are formed from the oxidation of dietary foodstuffs. If, for example, we take in excess calories, the level of ROS that escapes from the respiratory chain antioxidant regulation may rise 5 to 10-fold [2]. This results in radical damage and diseases such as Metabolic Syndrome (MS) that includes obesity, heart disease and diabetes and other inflammatory disorders [3]. There are a number of exogenous sources of free radicals such as ultraviolet-light irradiation, smoking, drugs, mutagens, carcinogens, allergens, pesticides, and other environmental agents, as well as certain anthropogenic activities that also contribute to antioxidant defense erosion.

Regardless of the source of free radicals, they can attack any of the major constituents of the cell. They are particularly reactive with lipids and the reactions shown in Equations 1 to 3 results in formation of Lipid Hydroperoxides (LHP) (PUFA-O-OH) [4]. In equation 1 a free radical (R·) attacks a Polyunsaturated Fatty Acid (PUFA) to form a Polyunsaturated Fatty Acid radical (PUFA·). This radical reacts with molecular oxygen to form fatty acid peroxy radicals (PUFA-O-O•) that, by hydrogen abstraction from an adjacent PUFA, yields unsaturated hydroperoxides (PUFA-O-OH). In this reaction, Equation 3, the newly formed PUFA radical propagates a chain reaction (autocatalysis) that results in extensive disruption of the cell's membranes.

$$R\cdot + PUFA \rightarrow PUFA\cdot + RH \quad \text{Eq.1}$$

$$PUFA\cdot + O2 \rightarrow PUFA\text{-}O\text{-}O\bullet \quad \text{Eq. 2}$$

$$PUFA\text{-}O\text{-}O\cdot \rightarrow PUFA\cdot + PUFA\text{-}O\text{-}OH \quad \text{Eq. 3}$$

The cells' architecture is one of the natural defense mechanisms against the deleterious effects of free radical attack. The level of free radical oxidation is the main biochemical process that determines barrier, structure, and matrix function of cell membranes. As noted, biological membranes are rich in lipids and present a vulnerable target for free radical attack that leads to autocatalytic lipid peroxidation, as described above. Persistent disorder and imbalance of free radical oxidation products, as manifested by lipid hydroperoxides, leads to membrane dysfunction and disease development. Thus, the concept of incipient and later stages of disease, based upon lipid peroxide/antioxidant homeostasis, has emerged.

Materials and Methods

Clinical and lipid/antioxidant homeostasis data were compiled from research of the late Professor Vera Podoprigorova and colleagues from a range of inflammatory disorders and diseases [5-11].

Table 1: Diagnosis. Patient Parameters and Lipid Hydroperoxide/Antioxidant Homeostatic Imbalance. Clinical Diagnosis; number in each class of disorder; number of male/females, and age (age range or mean age ± S.D.); and increase (%) above control Lipid Hydroperoxide level and decrease in antioxidant activity is provided. Significance is based upon comparisons of change of each disorder compared to control.

Diagnosis	N	MALE/FEMALE	AGE	LPH/AOA	SIGNIFICANCE
Heal hy	129	118/28	22-56	LHP=63.6 ± 1.16 AOA=33.7 ± 1.02	---
Pelvis Inflammation	373	All Female	24.6 ± 3.2	LHP ↑ 115% AOA↓77%	NS
Pneumonia	50	Not indicated	20-50	LHP ↑ 114% AOA ↓ 76%	NS
Stomach Ulcer	36	Not indicated	39.19 ± 1.25	LHP ↑ 119% AOA ↓ 56%	$P \leq 0.05$
Duodenal Ulcer	120	Not indicated	39.19 ± 1.25	LHP ↑ 133% AOA ↓ 57%	$P \leq 0.05$
Rheumatic Diseases	66	18/48	45 06 ± 14.0	LHP ↑ 127% AOA ↓ 21%	$P \leq 0.05$
Severe Bronchial Asthma	30	10/20	34.79 ± 1.36	LHP ↑ 144% AOA ↓ 13%	$P \leq 0.001$
Liver Cirrhosis	12	All Males	50.2 ± 5.0	LHP ↑ 150% AOA ↓ ≥ 99%	$P \leq 0.001$

Vera G Podoprigorova was Professor and Chief of the Department of Propaedeutic of Internal Diseases and Chief of the Problem Laboratory of Clinical Biophysics and Metabolic Therapy at Smolensk State Medical University, Smolensk, Russia. Natalia Chaikovskaia is the daughter of Professor Podoprigorova and is continuing with her mother's research.

Patient population: Consisted of 373 diagnosed with small pelvis inflammation; 50 with Pneumonia; 36 with Stomach Ulcer Disease; 120 with Duodenum Ulcer Disease; 66 with Rheumatic Diseases; 30 with severe Bronchial asthma; and 12 with Liver Cirrhosis. 129 healthy patients served as Control. Patient population is further described in Table 1.

Lipid peroxidation values (Lipid Hydroperoxide (LHP) and Antioxidant Activity (AOA) were determined to be 63.6 ± 1.16 and 33.7 ± 1.02, respectively, obtained from 129 healthy individuals. A subset of healthy sera donors, consisting of 48 males and 16 females, ages 22 to 56, were examined for age, gender, and serum donor frequency influence on LHP and AOA. There were no gender differences in LHP between males and women of age 31 and greater, although there was a significant difference in women under age 31. There were no gender differences in AOA due to age or serum donor frequency [11].

Lipid Hydroperoxide/Antioxidant Analysis: Parameters of hydroperoxide/antioxidant homeostasis in blood serum from each patient of the subject groups were determined by rhodamine G activated chemiluminescence in the presence of Fe (II+) [12- 14]. Fasting blood was drawn from each patient and, after 30 min incubation at 37°C, serum was prepared following 10 min low speed centrifugation in a clinical centrifuge (RCF=2325 × g).

Chemiluminescence investigations were conducted at 37°C with a chemiluminometer fitted with photoelectronic multiplier. Test ingredients were thoroughly mixed and chemiluminescence was initiated with the addition of 0.5 ml 25 mmol solution of FeSO4 and 0.1 ml distilled H2O. Standard signals of quick (Aq) and slow (As) flashes were detected, and amplitudes recorded. These steps were repeated using 0.1 ml of blood serum and flash amplitude changes (Δ) from the initial standard were used to determine hydroperoxides and antioxidant status using the following formulae:

$LHP = Aq^{\Delta}$, mm/Aq, mm × 100

Direct dependence between the level of oxidative processes and concentration of free radicals was reported by Miyazawa et al. [15]. Changes of the As^{Δ} flash is inversely proportional to the sum of the Antioxidant Activity (AOA).

AOA = (As-AsΔ)/As × 100

Lipid Hydroperoxide/Antioxidant Ratio: LHP/AOA ratios were calculated from the average per cent increase in LHP and decrease in AOA of each disorder class (Table 1).

Statistical Analysis: Comparisons of mean values of LHP and AOA for each patient group with control (healthy) group were made with Student's t-test, with significance based upon P-values of 0.05 or smaller. Table 1 reports the statistical significance of LHP/AOA for each patient population compared to control.

Results and Discussion

Lipid peroxide homeostasis - proof of principle

Lipid Hydroperoxide/antioxidant homeostasis, in relation to clinical condition, is depicted in Charts 1, 2. In the case of inflammatory disorders, small pelvis inflammation and pneumonia, both exhibited about a 15% increase in LHP while AOA decreased roughly 25% (Chart 1). Both indicators were statistically non-significant from control. After treatment and recovery, these indicators returned to normal if the homeostasis systems eliminated the insulting stress factor(s).

Dysfunctions of different organs or chronic inflammation are often observed in the Incipient Disease Stage I. Significant changes in the levels of peroxide homeostasis begin appearing in this stage. In the case of stomach and duodenal ulcer, AOA decreases approximately 43%. LHP increases up to 119% in stomach ulcer and 133% in duodenal ulcer.

Further worsening of the LHP/AOA homeostatic imbalance leads to greater suppression of the protection mechanisms with evident organ and structural damage, as exemplified in the frank Degeneration Disease Stage II. Thus, in the case of Rheumatic diseases and Severe Bronchial Asthma, AOA decreases approximately 80% to 85%. LHP increases 27% to 44% for Rheumatic diseases and Asthma, respectively.

In the Terminal Disease Stage III, e.g., liver cirrhosis, AOA dropped ≥ 99% and LHP increased up to 150%. The relationship of each disorder stage to LHP/AOA ratio (an indication of the state of LHP/AOA homeostasis) is depicted in Chart 2.

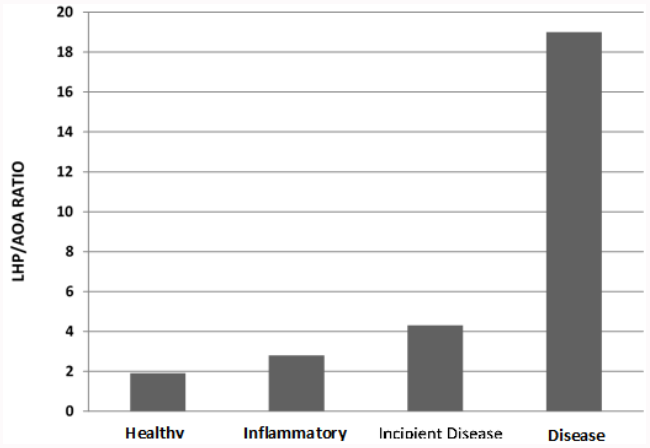


Chart 1: Relation of lipid peroxide/antioxidant homeostasis to classification of disorder.
Imbalance of lipid peroxidation and antioxidant homeostasis in relation to disorder classification can readily be recognized from the ratio of lipid hydroperoxide formation and. Antioxidant activity. Incipient Disease is a dysfunctional state and represents Stage 1 of Disease.

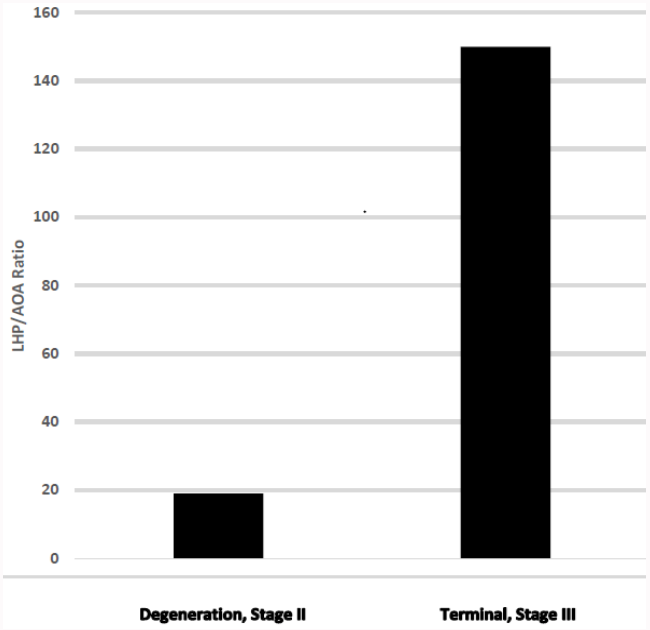


Chart 2: Relation of the ratio of Lipid Peroxide/antioxidant Homeostasis to disease stage. Solid bars depict the LHP/AOA ratios of disease stages II Degeneration, and stage III Terminal.

It should be noted that in peroxide homeostasis studies, it was observed that some traditional medical treatments directed to symptom suppression, often aggravated oxidative stress conditions. As example, after standard treatment of stomach ulcer disease, AOA decreased a further 10% and LHP increased approximately 5%. In the case of pneumonia, treatment actually moved patients from the Inflammatory class to Incipient Disease Stage I. On the other hand, using physical influence, e.g., microwaves, stimulation of natural protection forces enhanced the health situation [10]. Microwave treatment of pneumonia patients increased AOA 30% and LHP decreased 20%. Thus, measuring LHP/AOA status has significant diagnostic and treatment importance.

Oxidative stresses is known to be due to both endogenous and exogenous stress factors and are involved in the etiology of several major disorders [16-19]. The development of Oxidative Balance Scores (OBS), based on different anti- and pro-oxidant components (mainly nutrients and life-style changes), has been associated with reduced risk of a few diseases [20]. However, the criteria for defining and verifying appropriate OBS have yet to be determined, and this long-term approach to good health is preventive and restorative in nature.

Conclusion

Based upon the ancient Greek theory that disease results from equilibrium imbalances between bodily forces and the assaults of endogenous and exogenous stress factors, herein is proposed a novel and rational approach to classifying and staging diseases and following their development. Persistent insult from free radical attaches leads to membrane dysfunction and disease development. Measuring Lipid hydroperoxide/antioxidant homeostasis provides a direct diagnostic insight into a broad range of disorders ranging from inflammatory status to terminal stage of disease. Although showing potential, the general utility of LHP/AOA ratios as a diagnostic tool must await accrual of a broader, comprehensive data base. However, the utility of these ratios has an immediate and important role in medical practice. First, the LHP/AOA ratio can be used to determine the progress of disease. Is the disease at the dysfunctional or terminal stage? Second, the ratios can be useful in following the progress of the disease. Third, the ratios can provide insight into potential intervention and therapeutic strategies. Finally, the ratios could provide a measure of the efficacy of these strategies. A clinical test for the measurement of LHP/AOA ratios would add greatly to the physicians' armamentarium.

References

1. Sarton G. A History of Science. Ancient science through the Golden Age of Greece. Harvard University Press, Cambridge. 1952.
2. Turrens JF, Freeman BA, Crapo JD. Hyperoxia increases H2O2 release by lung mitochondria and microsomes. Biochem Biophysics. 1982;17(2):411-21.
3. Alberti RG, Zimmet P, Shaw J, International Diabetes Federation (IDF) Epidemiology Task Force Consensus Group. The metabolic syndrome - a new worldwide definition. Lancet. 2005;366:1059-62.
4. Black HS. Potential involvement of free radical reactions in ultraviolet light mediated cutaneous damage. Photochem Photobiol. 1987;46(2):213-21.
5. Podoprigorova VG, Tsigankova GM, Farashuk NF. The specific features of the cytolytic syndrome in patient with chronic diffuse liver in relation to the severity of a pathological process. Clin Lab Diagn. 2006;1:15-8.
6. Podoprigorova VG, Bobilev AA, Maksakova TS. Oxidative-antiradical parameters of bronchial asthma control. Questions of Biological Medicine and Pharmaceutical Chemistry. 2007;3:44-9.
7. Podoprigorova VG, Bobilev AA, Ivanova SM, Speranskii AI. Disregulation of oxidative and autoimmune processes at patients with lupus and rheumatoid arthritis. Biomed Chem. 2005;51:(5)536-41.
8. Stepankova SA, Nikiforovskii NK, Podoprigorova VG, Stepankova TA. Free radical and antioxidant status condition and correction of their disorders in case of acute small pelvis organs inflammation. Obstetr Gynaecol. 200;4:41-5.
9. Ivanishkina EV, Podoprigorova VG. Sanogenetic effects of millimeter-range electromagnetic radiation in community-acquired pneumonia. Pulmonology. 2010;3:92-6.
10. Podoprigorova VG, Ivanishkina EV. Study of microwave resonance

therapy with flowing frequency effects at duodenum ulcer disease patients (open control randomized study). Biomed Technol Radioelectronics. 2005;6:14-8.

11. Podoprigorova VG. Oxidative stress and ulcer disease (Monograph), Moscow "Medicine", 2004.
12. Boveris A, Cardenas E, Reiter R, Filipkowski M, Nakase Y, Chance B. Organ chemiluminescence: Noninvasive assay for oxidative radical reactions. Proc Natl Acad Sci USA. 1980;77(1):347-51.
13. Vladimirov IuA, Suslova TB, Olenev VI. Chemiluminescence associated with the formation of lipid peroxides in biological membranes. II. The role of Fe2+ in the development of chain oxidation of lipids and ultra-weak luminescence. Biofizika. 1969;14(5):836-45.
14. Sherstnev MP, Atanaev TB, Vladimirov IuA. Chemiluminescence activated by rhodamine G in plasma in the presence of divalent iron ions. Biofizika. 1989;34(4):684-7.
15. Miyazawa T, Fujimoto K, Kanego T. Lipid peroxidation and chemiluminescence in animal tissues. J Am Oil Soc. 1986;63:429-31.
16. Maritim AC, Sanders RA, Watkins JB 3rd. Diabetes, oxidative stress, and antioxidants: A review. J Biochem Mol. 2003;17(1):24-38.
17. Pignatelli P, Menichelli D, Pastori D, Violi F. Oxidative stress and cardiovascular disease: New insights. Kardiol Pol. 2018;76(4):713-22.
18. Klaunig JE. Oxidative stress and cancer. Curr Pharm Des. 2018;24:4771-8.
19. Roberts CK, Sindhu KK. Oxidative stress and metabolic syndrome. Life Sci. 2009;(21-22):705-712.
20. Hernandez-Ruiz A, Garcia-Villanova B, Guerra-Hernandez E, Amiano P, Ruiz-Canela M, Molina-Montes E. A review of a priori defined oxidative balance scores relative to their components and impact on health. Nutrients. 2019;11(4):774.