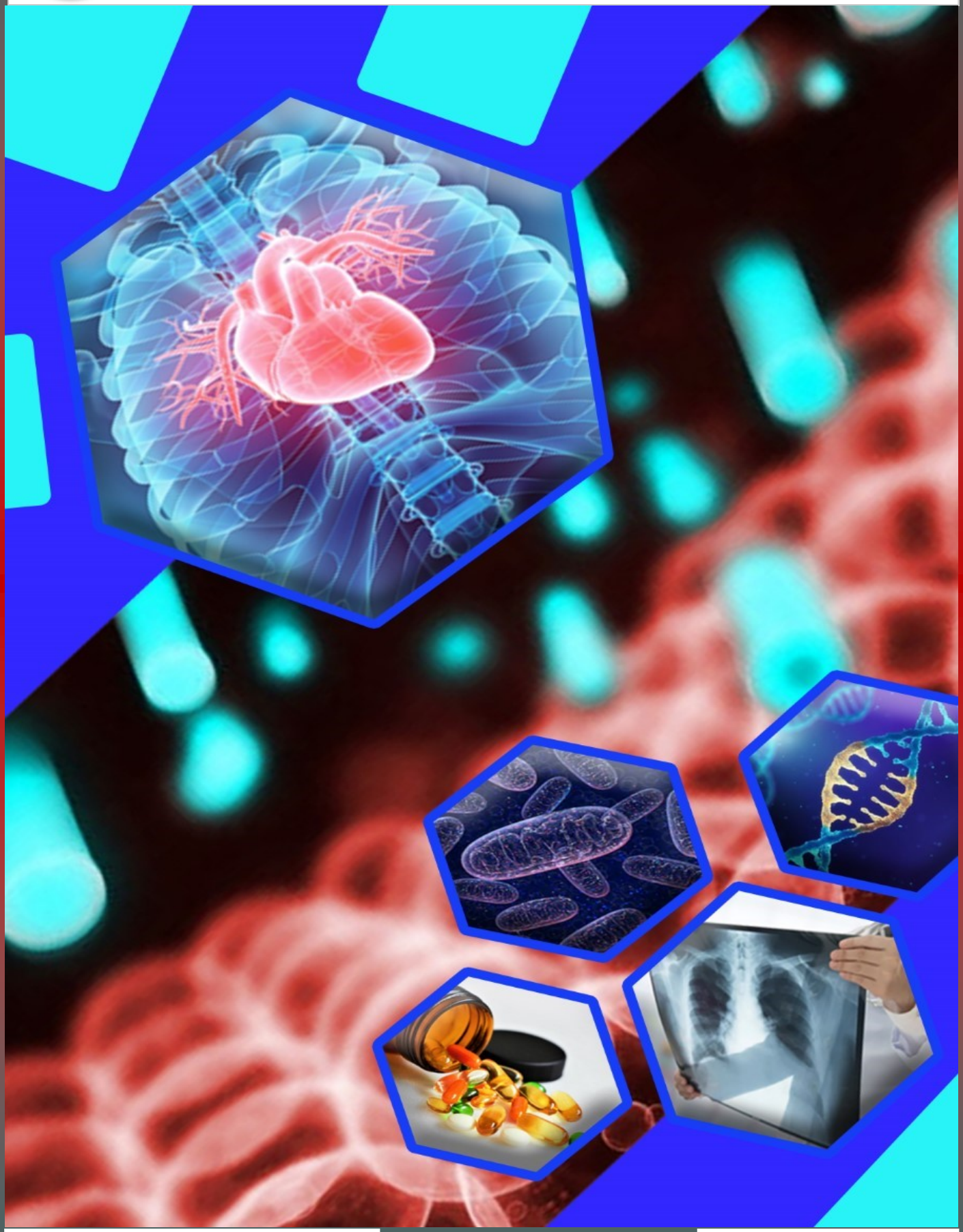
Kuwait Pharmacy Bulletin

DRUG INFORMATION FOR THE HEALTH PROFESSIONAL



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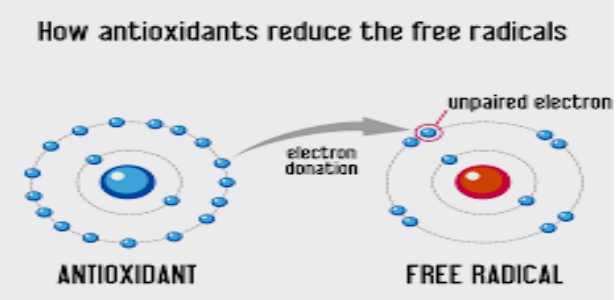
Targeting oxidative stress and free radicals in cardiovascular diseases as a potential therapeutic strategy

Reactive oxygen species (ROS), also known as oxygen radicals, are compounds produced during mitochondrial oxidative metabolism or generated due to cytokines, xenobiotics and bacterial infections (1). Examples of ROS are shown in Table 1. The human body has multiple sources of oxygen radicals. Examples of reactions that can generate hydroxyl radicals include lysing water by UV or x-rays and eventually forming hydroxyl radicals, and non-enzymatic reactions of metal ions such as Cu^{+}, Co^{2+}, Ni^{2+}, and Fe^{2+} with oxygen or hydrogen peroxide (2). Nitric oxide (NO), which plays a critical role in cell signaling, is considered a radical itself and can react with superoxide to give peroxynitrite, that degrades to form hydroxyl radicals (2). Over-production of NO and reactive nitrogen species (RNS) result in nitrosative stress which is similar to oxidative stress (OS) in the manner of damage caused. The ROS can have a normal physiological effect or they can be damaging and lead to oxidative injuries in the biological system causing oxidative stress.

Oxidative stress



Oxidative stress is a state of imbalance due to an excess of oxygen radicals over the ability of the cells to defend against them with endogenous antioxidants (2). The body under normal conditions can get rid of these ROS through antioxidants, but the failure of doing so gives the ROS opportunity to damage the lipids in cell membranes, plasma lipoproteins, proteins and DNA.

Table 1. Main reactive oxygen species (ROS)

$O_2^{\cdot -}$	Superoxide radical
H_2O_2	Hydrogen peroxide
OH	Hydroxyl radical
$^1O2$	Singlet oxygen
HOO•	Hydroperoxyl radical
LOOH	Alkylhydroperoxide
LOO•	Alkylperoxyl radical
LO•	Alkoxyl radical
CIO-	Hypochlorite ion
$Fe^{4+}O$	Ferryl ion
$Fe^{5+}O$	Periferryl ion
NO•	Nitric oxide

Free radical scavenging mechanisms and the antioxidant defence system

Antioxidants and their mechanism

The term "antioxidant" refers to a mechanism that is shared between multiple components as a defence against oxidative stress (3).

These antioxidants are molecules with the ability to react with radicals to block their effects either by deactivating the enzymes that generate them or increase their activity, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase (XO), or via increasing the level and expression of the antioxidant enzymes that neutralise them, like catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase GPX)(3).

In another way, they inhibit or neutralise the free radicals directly or turn them into less active and less dangerous moieties (3). Antioxidants neutralise free radicals either by giving or accepting electron(s)

In this issue

Table 2 Enzymatic Antioxidants (4)

Enzymatic antioxidant	Cellular location	Substrate	Reaction
Zn/Cu/Mn SOD	Mitochondrial matrix (Mn SOD) cytosol (Cu/Zn SOD)	$O_2^{\cdot -}$	$O_2^{\cdot -} \rightarrow H_2O_2$
CAT	Peroxisomes cytosol	H_2O_2	$2H_2O_2 \rightarrow O_2 + H_2O$
GSHPx	Cytosol	H_2O_2	$H_2O_2 + GSH \rightarrow GSSG + H_2O$
Prx–I	Cytosol	H_2O_2	$H_2O_2 + TrxS_2 \rightarrow Trx(SH)_2 +$

Mn: manganese, Cu: copper, Zn: zinc, SOD: superoxide dismutase, CAT: catalase, GSHPx: glutathione peroxidase, Prx-I: peroxiredoxin-I, O_2•- : superoxide, H_2O_2: hydrogen peroxide

to terminate the unpaired status of these radicals, and eventually inhibit cellular damage. They are found endogenously inside the body (intracellularly and extracellularly) or in the environment in food or vitamin supplements (4). These molecules can be categorised into enzymatic and non-enzymatic antioxidants.

Enzymatic antioxidants

The main cellular defence against ROS is antioxidant enzymes that facilitate the removal of superoxide ion and hydrogen peroxide, namely SOD, CAT and GPX/GSHPx (5).There is no enzyme-scavenging mechanism for the hydroxyl radical. It is a multi-step process that occurs when co-factors like copper, zinc, and manganese are available (5). The antioxidant enzymes convert harmful oxidative compounds to the less reactive H_2O_2 and then to H_2O. Table 2 shows the enzymatic antioxidants, their locations, and the reactions they perform in a summarised form.

SOD comes in variable forms. The SOD in the mitochondria contains manganese (MnSOD), while the cytosolic has zinc and copper (CuZnSOD). It catalyses the transformation of two superoxide ions to oxygen and H_2O_2 (formula 1) (6). On the other hand, CAT, which is present in peroxisomes, converts H_2O_2 to water and oxygen (formula 2) (7). The enzyme GPX, which is found intracellularly and extracellularly, forms water and an oxidised glutathione or glutathione disulfide (GSSG) (formula 3 and 4). Glutathione peroxidase is a selenium-dependent enzyme that has strong activity towards both H_2O_2 and lipid peroxides (8). Then GSSG is quickly reduced to GSH by glutathione reductase which is NADPH-dependent enzyme (Fig 1) (9)

$$2O_2^{\cdot -} + 2H^+ \longrightarrow H_2O_2 + O_2 \text{ (formula 1)}$$

$$2H_2O_2 \xrightarrow{CAT} 2H_2O + O_2 \text{ (formula 2)}$$

$$H_2O_2 + 2GSH \xrightarrow{GPX} GSSG + 2H_2O \text{ (formula 3)}$$

$$\text{For lipid peroxides: } L\text{-}OOH + 2GSH \xrightarrow{GPX} GSSG + L\text{-}OH + H_2O \text{ (formula 4)}$$

Non-enzymatic antioxidants

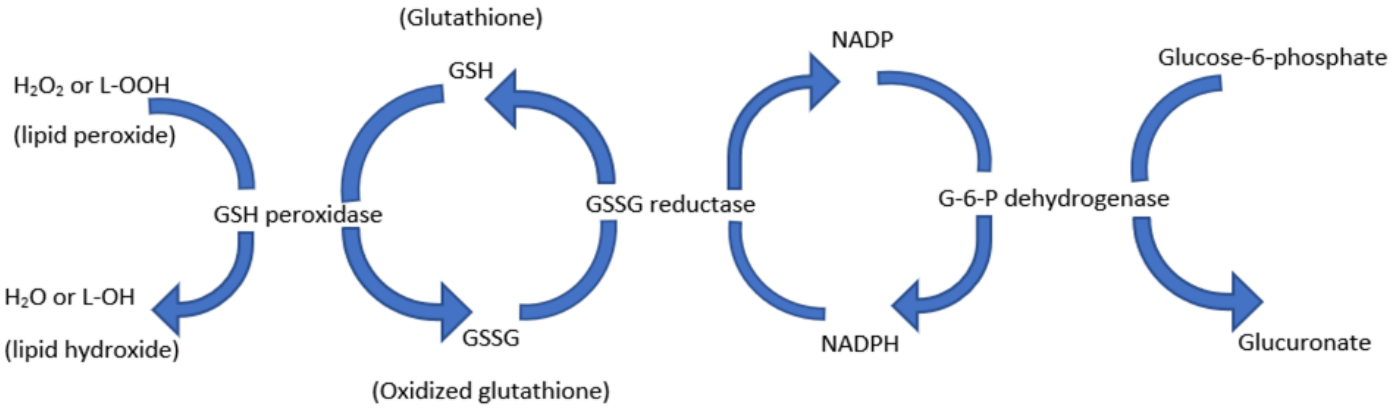


Figure 1: The glutathione oxidation-reduction (redox) cycle showing its important role in reducing harmful intracellular hydroperoxides involving lipid peroxides and hydrogen peroxides (5).

Non-enzymatic antioxidants are categorised into natural and synthetic antioxidants that prevent free radical chain reactions (4). Natural antioxidants such as vitamin C, vitamin E, uric acid and glutathione have an essential role as cellular antioxidants. Other examples of natural antioxidants are carotenoids, hydroxycinnamates, theaflavin, theaflavin-3-gallate, allicin, piperine, and curcumin (4). Synthetic antioxidants, such as tert-butylhydroxyl-toluene, tert-butylhydroxyanisole and tert-butylhydroquinone, are commonly used in the food industry to inhibit lipid oxidation (10).

Vitamins

Vitamins are categorised under natural non-enzymatic antioxidants; the two most widely studied are vitamin C (ascorbic acid) and vitamin E (α-tocopherol). Vitamin C is a hydrophilic free-radical scavenger, and a reducing agent which neutralises ROS (4). It also gives an electron to lipid peroxide in order to stop the continuous lipid peroxidation chain reaction by changing to ascorbate radical (4). Following that, ascorbate paired radicals react in a rapid way to give a single molecule of ascorbate and a single molecule of dehydroascorbate that has no antioxidant activity, so it turns back to ascorbate through adding two electrons by an oxidoreductase (4).

Vitamins C and E cooperate to produce α-tocopherol from α-tocopherol radicals in cellular membranes and lipoproteins. In addition, vitamin C protects the protein thiol group from oxidation by increasing intracellular levels of glutathione. Notably, it is capable of keeping its reduced form inside the cell by reacting with glutathione that is catalysed by glutaredoxins and protein disulfide isomerase (4).

Vitamin E, is a hydrophobic molecule that acts within the lipid phase. It has the capability, alongside vitamin C in the aqueous phase, to neutralise hydroxyl, alkoxyl and lipid peroxyl radicals and produce lipid hydroperoxides, water and alcohol (formula 5) (11). The tocopheroxyl radical, which is relatively stable in normal conditions, does not have enough power to start lipid peroxidation alone, making it a beneficial antioxidant (11).

Carotenoids

Carotenoids are lipid soluble phytonutrients with long unsaturated alkyl chain making them highly lipid-soluble. Due to their structure, they can scavenge the peroxyl from the lipid peroxidation chain more efficiently than other ROS (12). They also have a special and essential role in protecting cell membranes and lipoproteins from free radicals. The most important one in this class is α-carotene, which is an effective singlet oxygen scavenger but can also trap peroxyl radicals with little oxygen pressure similar to α-tocopherol (4). By forming resonance stabilized carbon-centred radical adducts, carotenoids inhibit peroxyl radicals (4). More importantly, β-Carotene shows antioxidant property due to its chemical configuration and the interaction with cellular membranes (13).

Uric acid and Glutathione

The uric acid and glutathione in the plasma are considered physiological antioxidants. Uric acid is the most abundant water-soluble antioxidant in the body (14). It demonstrates strong scavenging ability in aqueous medium towards carbon-centred and peroxyl radicals but loses its ability in lipid membranes (15). Importantly, uric acid cannot scavenge superoxide radical but can scavenge peroxynitrite extracellularly in the presence of ascorbic acid and thiols (16).

Glutathione on the other hand, is a multifunctional intracellular antioxidant because of the sulphur atom that can readily compensate for the loss of a single electron (3). It is found in large quantities in the cytosol, nuclei and mitochondria, and plays a protective role against oxidative/nitrosative stress as a co-factor for many antioxidant enzymes, participates in amino acid movement across the plasma membrane, scavenges hydroxyl radical and superoxide, and also regenerates the active forms of vitamins C and E (3).

Role of oxidative stress in the cardiovascular system diseases

Vascular endothelium dysfunction

Vascular oxidative stress and the increase in ROS production, especially superoxide, play an important role in vascular endothelial dysfunction and also in multiple cardiovascular diseases (CVDs) and conditions including atherosclerosis, hypertension, myocardial infarction, and ischemic injury (17). Vascular enzymatic superoxide sources are NADPH oxidase, xanthine oxidase, mitochondria, and sometimes eNOS (18). Few examples of extra-cardiac and extra-vascular systems as OS triggers under pathophysiologic stimulation are sympathetic nervous system (SNS) activation that will increase the norepinephrine (NE) level and eventually lead to OS (17). Also, the activation of renin-angiotensin-system (RAS) that will increase the level of Ang II is another example. Endothelial dysfunction can cause OS and vice-versa, as well as neutrophils acti vation that increases hypochlorous acid production resulting in oxidative damage. The net result as

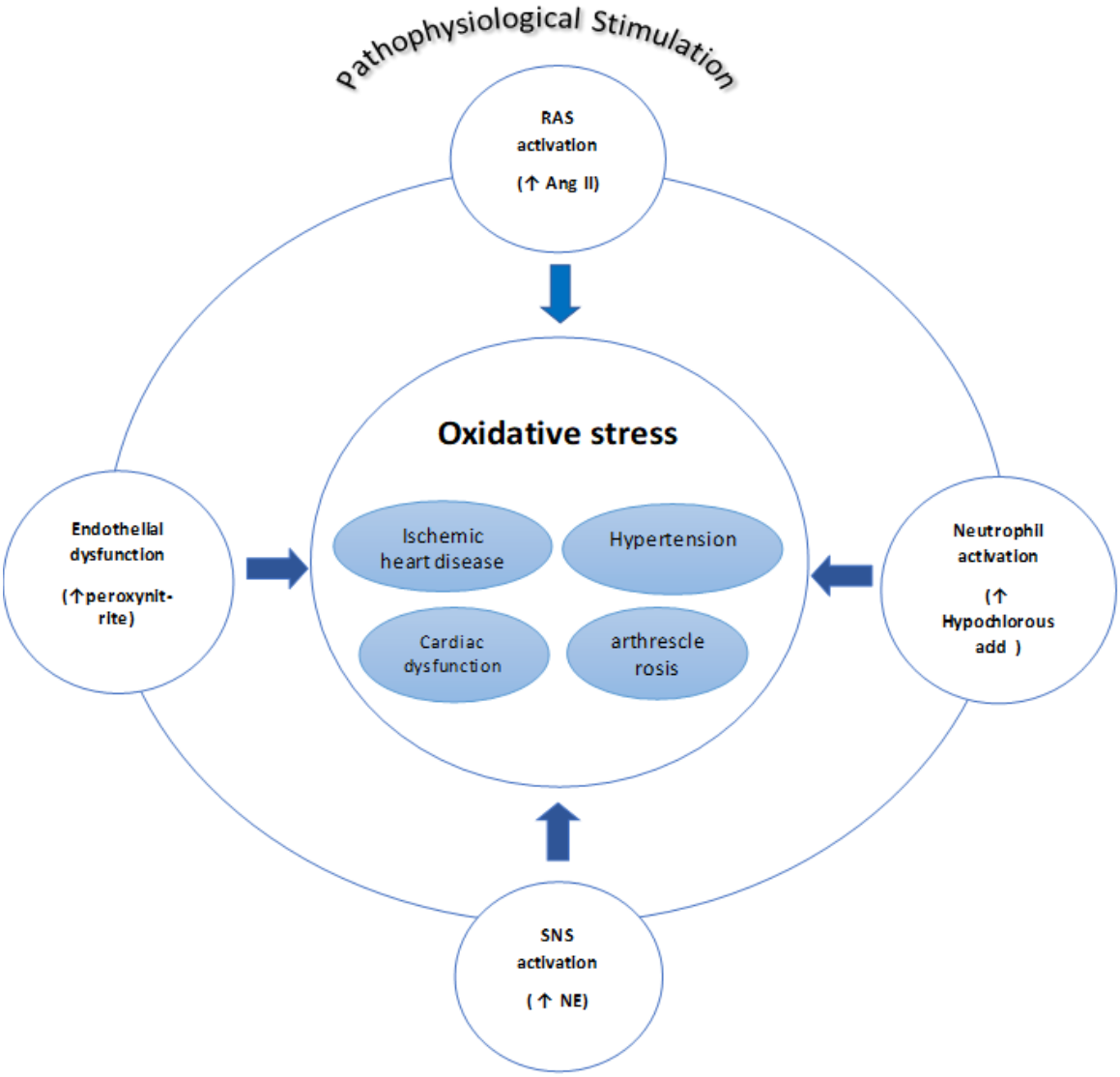


Figure 2: oxidative stress triggers and results

shown in Fig 2 is cardiac and vascular abnormalities manifesting as arrhythmias, cardiac dysfunction, atherosclerosis, and hypertension (17).

Endothelin-1 (ET-1), a strong vasoconstrictor, with pro-oxidant and pro-inflammatory activities that can contribute to endothelial dysfunction when it is over-expressed, increases the level NADPH oxidase activity that leads to oxidative stress. Its expression increases by Ang II stimulation, oxidised LDL (ox-LDL), ageing process and diabetes mellitus (19). ET-1 can directly increase albumin permeability in the glomeruli and renal inflammation through ETA receptor activation (20) as well as aortic vascular cell adhesion molecule 1 (VCAM-1) and monocytes/ macrophages infiltration (21). It also increases intracellular calcium that leads to vasoconstriction and directly reducing the endothelial vasodilator properties by inducing the redistribution of eNOS from the plasma membrane to the mitochondria by by eNOS phosphorylation eventually reducing NO bioavailability (22).

Oxidative stress in Atherosclerosis

Disturbance in endothelial function is a distinctive feature found in patients with coronary atherosclerosis, and some reports mentioned that it may give a hint on the long-term progression of atherosclerotic disease as well as the rate CV events (18). Atherosclerosis results from the oxidation of LDL found in the arterial wall and produced by ROS. Ox-LDL uptake by macrophages is easier in comparison with non-oxidized lipoproteins. Smooth muscle cells and macrophages are the main origins of oxidative molecules and ROS in atherosclerotic vessels (23). In turn, LDL-oxidation triggers adhesion molecules expression, smooth muscle cells proliferation and migration, lipids oxidation, and endothelial dysfunction as apoptosis (24, 25). Further, ox-LDL affects the release of some cytokines, such as IL-1β, IL-6 and TNF-α, that are responsible for the acute inflammatory processes. Oxidative stress, in particular, H_2O_2,

also participates in atherogenesis by generating transcription factors, such as nuclear factor κB (NF-κB) and activator protein 1 that help in the expression of adhesion molecules like VCAM-1, ICAM-1, and some cytokines working in smooth muscle cells of atherosclerotic vessels (26). H_2O_2 can produce hydroxyl radicals if metal ions are present and can increase phosphorylation of tyrosine kinases, leading to more of neutrophil cells binding on the endothelium and alteration of vessel permeability (25).

Evidence suggests that common risk factors for atherosclerosis like hypercholesterolemia, diabetes mellitus, arterial hypertension, smoking, age, and nitrate intolerance, may not only increase the risk of generating ROS from endothelial cells, but also from the smooth muscle cells and the adventitial cells (25).

Oxidative stress in hypertension

Free radicals are now proven to have a role in the pathogenesis of hypertension due to reports made in patients with essential hypertension of elevated levels of superoxide and hydrogen peroxide and the treatment of the Dahl salt-sensitive rats with a diet high in salt resulted in elevated levels of H_2O_2 (27).

Also, it was reported that patients with hypertension had low concentrations of free radical scavengers like vitamin E, SOD, and GSH (28). Vasoconstriction was noticed in hypertensive rats due to the release of thromboxane A2 in the aortic smooth muscle under the influence of free radicals (29). The activity of NOS, in neutrophils, was reported to decline in hypertensive patients (30). The RAS has been shown to induce OS in endothelial and vascular smooth muscle cells and might be an essential mechanism underlying the pathophysiology of hypertension (31). Ang II was given experimentally to rats to make them acutely hypertensive; later on, the rats displayed extensive and severe endothelial and smooth muscle lesions that was prevented by antioxidant therapy (31). Such outcomes advocate that free radicals participate in the pathogenesis of vascular hyperpermeability and cellular damage (31). The importance of ACE inhibitors lies in their ability to inhibit angiotensin I conversion to angiotensin II, thereby reducing the oxidative stress caused by Ang II (32).

Oxidative stress in heart failure

ROS and RNS accumulation in the heart has been noticed and reported in multiple heart diseases (33). ROS/RNS generate from various intracellular sources, such as XO, NADPH oxidase and NOS, with mitochondria as the main source in cardiac myocytes (34, 35).

Mitochondrial respiration produces superoxide via electron leakage at the complexes I and III of the electron transport chain (ETC), which are transferred to free O_2. Mitochondrial SOD then dismutases the superoxide to hydrogen peroxide, and it can be further reduced to give $OH^{\cdot}$ if free iron is available (Fenton reaction) (36).

As mentioned before, superoxide produces peroxynitrite ($ONOO^{\cdot}$) in the presence of nitric oxide ($NO^{\cdot}$) (33). Notably, the metabolism of certain medications and xenobiotics including anti-cancer medications, doxorubicin (37), can generate ROS which has been involved in the development of cardiomyopathies (38).

Despite the reports of elevated ROS levels in heart failure (HF) patients, it is unclear how they are produced and accumulated (39). One possibility is succinate (a Krebs intermediate) accumulation during cardiac ischemia that is considered enough to produce large amounts of ROS through induction of reverse electron transport in the ETC during reperfusion (40).

This metabolic action has been viewed as an important process responsible for ischemia-reperfusion injury, therefore, a potential therapeutic target in ischemic heart diseases (40). Yet its long-term effect on ischemic cardiomyopathy or HF remains unknown (33). Those with HF with reduced ejection fraction (HFrEF) seem to have various sources of ROS compared to those with preserved ejection fraction (HFpEF) (33). In HEpEF, endothelial cells participate in the production of ROS, while cardiomyocytes have been recognised as the major source of ROS in HFrEF (35).

Calcium overload is an important key player in HF and has been associated with elevated ROS release and decreased ATP generation (41). The link between calcium and ROS production in mitochondria is that calcium activates Krebs cycle dehydrogenase that is associated with the oxidative phosphorylation, sustaining a reduced NADH pool and contributing to cellular energy homeostasis and maintaining adequate cardiac work (42).

Moreover, this process is inhibited in HF leading to disruption of mitochondrial Ca^{2+} uptake and then ROS generation and accumulation. This results from a conversion in the action of the mitochondrial enzyme nicotinamide nucleotide transhydrogenase (Nnt) in the heart under pressure overload (43). It converts NADH to NADPH, which is an important substrate for antioxidant enzymes. When there is an overload condition, Nnt catalyses the opposite reac-

tion, that decreases the antioxidant activity (33).

Strategies to target oxidative stress in the cardiovascular system

The CVDs including hypertension, ischemic heart diseases, and heart failure are the leading cause of death around the world (44). It was proven that oxidative/nitrosative stress has a role in the underlying pathology of the CVDs and this led to many questions about whether or not OS could be a feasible therapeutic target. Knowing the mechanism of oxidative stress-induced damage to the CVS has given a view to what possibly can be targeted for the therapy.

Few strategies are currently available for this purpose such as natural and synthetic antioxidants supplementations (vitamin C, E, flavonoids), medications with antioxidant properties, and gene therapies.

Starting with natural/synthetic antioxidants, it has been found in pre-clinical studies on experimental models of hypertension that treatment with antioxidants like vitamin C and E or a combination of them was effective, but the efficacy was not proven in large clinical trials (18).

Another compound that received considerable attention is resveratrol, a natural non-flavonoid polyphenol antioxidant found in various types of plants mainly grapes, with preclinical studies showing that it has an effect not only on CVDs but also in cancer, diabetes and neurodegenerative diseases (45). This compound can decrease the activity of NADPH oxidase and downregulates it, thus decreasing ROS production. It also works on enhancing biosynthesis of BH_4, hence hindering production of superoxide radical from the uncoupled eNOS. In addition, it acts as a gene regulator that increases expression of antioxidant enzymes such as SOD, that in turn inhibits ROS production and enhances their elimination (45). Unfortunately, the clinical trials for resveratrol and other antioxidants are limited and the results of what is available are disappointing.

Medications like ACEi, AT-1 receptor blockers (ARBs) or statins have shown pleiotropic effects by their indirect antioxidant and anti-inflammatory properties that lower cardiovascular events (18). Statins were found to exert antioxidant effects that are independent from its lipid-lowering effect and improve the circulating vitamin E through reducing NADPH oxidase activity (46). Interestingly, the antidiabetic metformin appears to be a potential cardioprotective agent for myocardial ischemic injury through certain antioxidant enzymes signaling pathways (47).

Apart from the pharmacological approaches, gene therapy and viral over-expression of antioxidant enzymes have been considered as a strategy to target OS. Part of the DNA is introduced into cells using viral or nonviral vectors (48). Adeno-viral mediated over-expression of superoxide dismutase delivery to the brain in HF models improves the heart's status and mortality (49). Despite it being a great tool in experiments, it has limitations that restrain its potential clinical use, one of which is that adenoviruses trigger immune responses decreasing its effect in cardiovascular tissues (50).

Antioxidants in clinical practice

Vitamin C and E (natural and synthetic forms) are two of the most studied antioxidants in CVDs. Many in *vivo* and in *vitro* animal studies have been conducted but with controversial outcomes ranging from beneficial to deleterious or no effect.

One study conducted using a rat model with untreated renovascular hypertension with administration of vitamin C (150 mg/kg; intravenous) reported reduced heart rate, suggesting improvement in baroreflex sensitivity (51). Alpha-Tocopherol-Beta-Carotene Cancer Prevention study (ATBC) done in 1997 in smokers who had MI, receiving a dose of 50 IU of vitamin E, and Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease (SPACE) trial in 2000 in haemodialysis patients with dose 800 IU for secondary prevention of CV events resulted in reduction of non-fatal MI but fatal coronary endpoints were not reduced (52, 53).

Furthermore, in Antioxidant Supplementation in Atherosclerosis Prevention study randomised trial in 2000, vitamin E and slow-release vitamin C, were combined together for secondary prevention of CVD events for 3 years in subjects with elevated cholesterol levels. The result was a reduction in the progression of carotid atherosclerosis in men but not in women (54). A trial conducted in 2013, evaluated vitamin E and C combined, and vitamin C alone, and the result was that the combination of both enhanced endothelial-dependent vasodilation in patients with coronary artery disease and suggested it might be better than vitamin C alone (55).

Regarding dietary vitamin E and C, a meta-analysis of cohort studies was done involving 400,000 patients with high intake of vitamin E and vitamin C and the result was a decrease in the rate of coronary heart disease with high intake of dietary antioxidant vitamins (56). Aside from that, another trial tested the relationship of vitamin C intake from supplements versus food on early atherosclerosis observed by carotid intima-media thickness (IMT) and the result was that vitamin C taken from diet

decreased the process of IMT when compared to the supplemental one (57). Vitamin A and beta-carotene also underwent some clinical trials to determine whether or not they can target oxidative stress that is underlying the pathology of CV diseases. In one trial of vitamin A and beta-carotene results showed a lower incidence of atherosclerosis in patients receiving those antioxidants (58).

On the other hand, the American Heart Association (59) in 2004 and U.S. Preventive Services Task Force recommendation (60) discouraged the use of antioxidant vitamins supplement for the purpose of preventing CVDs because the scientific data still does not justify their use.

The Vitamin E Atherosclerosis Prevention Study in 2002 showed no benefit from vitamin E in subjects with elevated LDL-C levels in primarily preventing CV events but it did show a reduction in the circulating ox-LDL (61). One randomised trial using selenium for 4 months in 42 healthy males aged 18-45 years showed no significant effect on enhancing vascular responsiveness (62).

Regarding adverse events, the ATBC trial in 1994 used 29,133 males who were smokers and had no medical issues and tested with 50mg vitamin E for 6.1 years for primary prevention of CVDs, which resulted in an increase in hemorrhagic stroke (63). Another ATBC in the same year, but with beta carotene, showed an increase in overall mortality and more deaths because of ischemic heart disease, hemorrhagic stroke, and ischemic stroke (63).

The antioxidant cocktail has also shown an adverse effect in a couple of trials. The first was the Carotene and Retinol Efficacy Trial in 1996 on males using beta carotene and vitamin A for the purpose of primary prevention of CVDs but the unfortunate result was an increase in all-cause mortality and it had no effect on CVD mortality when it was tested in both men and women who were current or former smokers (64).

There have been a few studies with currently available medications as part of the strategies to target oxidative stress, but with controversial outcomes . Xanthine oxidase inhibitors, used to treat hyperuricemia, have been tested clinically for their effect in targeting oxidative stress in HF patients (65). Animals models with HF were tested and showed that allopurinol was effective in improving left ventricular ejection fraction (LVEF), counteracting left ventricular remodelling and decreasing endothelial impairment (66). In contrast, the Oxypurinol Therapy for Congestive Heart failure trial, a multicenter randomised, double-blind, placebo-controlled trial, put oxypurinol under examination as an adjunct therapy to the conventional one in 405 patients with moderate to severe heart failure using a dose of 600mg per day and it has not shown any benefit when the serum uric acid level is less than 9.5 mg/dL, however the effect was seen in those with higher serum uric acid in 108 patients. The same outcomes were observed in a study using allopurinol in HF patients (67).

There is still hope in this area of research and it is promising. The limitations have to be overcome by new strategies and carefully designed studies to meet the desired goals.

References

1.Cao JD, Kleinschmidt KC. Biochem Metabolic Principles. In: Nelson LS, et al, eds. Goldfrank's Toxicologic Emergencies, 11e.
2.Yoshikawa T. J Japan Med Assoc 2002;45(7):271-6.
3.Lu JM, et al. J Cell Mol Med. 2010;14(4):840-60.
4.Nimse SB, Pal D. RSC Advances. 2015;5(35):27986-8006.
5.Lodato RF. Chapter 45. Oxygen Toxicity. In: Tobin MJ, editor. Principles and Practice of Mechanical Ventilation, 3e.
6.Gough DR, Cotter TG. Cell death & disease. 2011;2:e213.
7.Zhan CD, et al. J Hypertension. 2004;22(10):2025
8.Heffner JE, Repine JE. Am Rev Resp Dis. 1989;140(2):531
9.Arthur JR. Cell & Molec Life Sciences. 2001;57(13):1825
10.Rababah TM, et al. J Agri & Food Chem. 2004;52(16):5183
11.Witting PK, et al. Biochemistry. 1997;36(6):1251-8.
12.Mueller L, Boehm V. Molecules (Basel, Switzerland). 2011;16(2):1055-69.
13.Riccioni G. Current Atherosclerosis Rep 2009;11(6):434-9.
14.Waring WS. QJM: Int J Med 2002;95(10):691-3.
15.Sautin YY, Johnson RJ. Nucl Nucl NuclAcids. 2008;27 (6):608-19.
16.Kuzkaya N, et al. Biochem Pharmacol. 2005;70(3):343-54.
17.Dhalla NS, et al. J Hypertension. 2000;18(6):655
18.Munzel T, et al. Eur Heart J. 2010;31(22):2741-8.
19.Smith JG. J Hypertension. 2012;30(9):1799–808.
20.Saleh MA, et al. Hypertension. 2010;56(5):942-9.
21.Barhoumi T, et al. J Hypertension. 2014;32(4):784
22.Sun X, et al. Am J Resp cell & Mol Biol. 2014;50(6):1084
23.Vogiatzi G, et al. Hellenic J Cardiol 2009;50(5):402-9.
24.Madamanchi NR, et al. Arteriosclerosis, Thrombosis & Vasc Biol. 2005;25(1):29-38.
25.Harrison D, et al. Am J Cardiol. 2003;91(3a):7a-11a.
26.Bourcier T, et al. J Biol Chem. 1997;272(25):15817-24.
27.Swei A, et al. Microcirculation. 1999;6(3):179-87.
28.Kumar KV, Das UN. Free Radical Res Com. 1993;19(1):59
29.Hibino M, et al. J Cardio Pharmacol. 1999;33(4):605-10.
30.Mehta JL, et al. Am J Cardiol. 1994;74(9):901-5.
31.Wilson SK. Circulation Res 1990;66(3):722-34.
32.Oskarsson HJ, Heistad DD. Circulation. 1997;95(3):557-9.
33.Kiyuna LA, et al. Free Radical Biol & medicine. 2018;129:155-68.
34.Burgoyne JR, et al. Circ Res. 2012;111(8):1091-106.
35.Munzel T, et al. Europ Heart J 2015;36(38):2555-64.
36.Nickel A, et al. Basic Res Cardiol. 2013;108(4):358.
37.Winterbourn CC. Nature Chem Biol.. 2008;4(5):278-86.
38.Octavia Y, et al. J Molec Cell Cardiol 2012;52(6):1213-25.
39.Seddon M, et al. Heart 2007;93(8):903-7.
40.Chouchani ET, et al. Nature. 2014;515(7527):431-5.
41.Santulli G, et al. PNAS. 2015;112(36):11389-94.
42.Cox DA, Matlib MA. J Biol Chem 1993;268(2):938-47.
43.Nickel AG, et al. Cell Metab 2015;22(3):472-84.
44.Top 10 Causes of Death 2016 [www.who.int/news-room/fact-sheets/detail/the-top-10-causes-ofdeath.

45.Xia N, et al. Br J Pharmacol. 2017;174(12):1633-46.
46.Cangemi R, et al. Europ Heart J 2007;29(1):54-62.
47.Wang X, et al. PLoS One. 2017;12(8):e0182777.
48.Rosenbaugh EG, et al. Am J Physiol Regul Integr Comp Physiol. 2013;304(11):R917-28.
49.Gao L, et al. Circulation. 2007;115(24):3095-102.
50.Descamps D, Benihoud K. Curr Gene Ther. 2009;9 (2):115-27.
51.Botelho-Ono MS, et al. Autonomic Neuroscience. 2011;159(1):38-44.
52.Rapola JM, et al. Lancet. 1997;349(9067):1715-20.
53.Boaz M, et al. Lancet. 2000;356(9237):1213-8.
54.Salonen JT, et al. J Int Med 2000;248(5):377-86.
55.Uzun A, et al. Cardiovasc J Africa. 2013;24(7):255-9.
56.Ye Z, Song H. Eur J Cardiovasc Prev Rehabil. 2008;15 (1):26-34.
57.Agarwal M, et al. Open Card Med J 2012;6:113-21.
58.D'Odorico A, et al. Atherosclerosis. 2000;153(1):231-9.
59.Kris-Etherton PM, et al. Circulation. 2004;110(5):637-41.
60.Moyer VA, Ann Intern Med. 2014;160(8):558-64.
61.Hodis HN, et al. Circulation. 2002;106(12):1453-9.
62.Hawkes WC, Laslett LJ. Am J Physiol Heart Circ Physiol. 2009;296(2):H256-62.
63.Massachussetts Medical Society. New England J Med. 1994;330(15):1029-35.
64.Omenn GS, et al. New England J Med. 1996;334(18):1150
65.Ahmed Z, Tang WH. Curr Heart Failure Rep. 2012;9(1):14
66.Bergamini C, et al. Europ J Heart Failure. 2009;11(5):444-5
67.Nasr G, Maurice C. J Cardiovasc Dis Res. 2010;1(4):191-5.

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TEST YOUR KNOWLEDGE

Answers on back page

1) Which of the following is a non-enzymatic anti-oxidant?

A. Peroxiredoxin
B. Catalase
C. Ascorbic acid
D. Superoxide dismutase

2) The natural, non-flavonoid polyphenol anti-oxidant that can decrease the ROS production

A. Resveratrol
B. Salicylic acid
C. Thiamine
D. Phytomenadione

3) Which of the following is not a source of vascular enzymatic superoxide?

A. NADPH oxidase
B. Xanthine oxidase
C. Mitochondria
D. Amylase

Is there a problem?
A patient taking atorvastatin is given the prescription below for additional treatment of his high levels of triglycerides. Is there any major error with the prescription?

ROX HOSPITAL

Patient Name: Ali Age: 55 years
Address: Street No: 62

Rx

Gemfibrozil tablet
600mg twice daily
Send one packet

Dr. Joshua
Signature Date: 10/03/20

Answer (Prescription Exercise)

Gemfibrozil may enhance the myopathic (rhabdomyolysis) effect of atorvastatin. The combination should be avoided.

Source: Uptodate (Lexicomp)

TOPICAL ISSUES AND CONTROVERSIES

Approved anti-tumour agents derived from nature

A large number of anti-cancer drugs derived from plant and marine organisms have been identified and approved during the last 60 years.

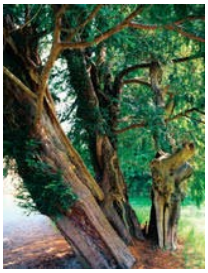
Anti-tumour products of plant origin

Alkaloids

Vinca monoterpene indole alkaloids originate from the Madagascar periwinkle plant (*Catharanthus roseus*). Vinblastine is commonly used to treat cancers such as Hodgkin's lymphoma. Vinblastine and vincristine have important pharmacological activities but are synthetically challenging.

Camptothecin (Camptosar and Campto) is a modified monoterpene indole alkaloid produced by certain plants (angiosperms). It is also produced by the endophytic fungus,*Entrophospora infrequens*, from the plant *Nathapodytes foetida*. In view of the low concentration of camptothecin in tree roots and poor yield from chemical synthesis, the fungal fermentation is very promising for industrial production. Camptothecin is used for recurrent colon cancer and has unusual activity against lung, ovarian, and uterine cancer.

Camptothecin's water-soluble derivatives irinotecan and topotecan are also used clinically. The cellular target is type I DNA topoisomerase. When patients become resistant to irenotecan, its use can be prolonged by combining it with the monoclonal antibody Erbitux (Cetuximab) which blocks a protein that stimulates tumour growth: the combination helps reduce metastatis in colorectal cancer patients expressing epidermal growth factor receptor (EGFR).



Taxol (paclitaxel), a diterpene alkaloid, has been very successful. Originally discovered in plants it is a fungal metabolite in *Taxomyces adreanae, Pestalotiopsis microspora*, *Tubercularia*sp. and *Phyllosticta citricarpa*. Originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), taxol showed anti-tumour activity but it took six trees of 100 years of age to treat one cancer patient.
Today, taxol is produced by plant cell culture or by semi-synthesis from taxoids.

More recent metabolic engineering has yielded a *S. cerevisiae* strain producing over 8 mg l-1 taxadiene and 33 mg l-1 of geranyl geraniol. The use of cells of the plant *Taxus chinensis* to produce taxol became the industrial means to make the compound.

Taxol is approved for breast and ovarian cancer and acts by blocking depolymerization
of microtubules. In addition, taxol promotes tubulin polymerization and inhibits rapidly dividing mammalian cancer cells.

Taxanes and camptothecins alone account for approximately one third of the global anti-cancer market.

An analogue of taxol, docetaxel (Taxotere) is approved in treatment of breast cancer, non-small cell lung cancer, advanced stomach cancer, head and neck cancer and metastatic prostate cancer. Docetaxel is more water soluble than paclitaxel.

Etoposide and teniposide

These two compounds were derived as semisynthetic derivatives of podophyllotoxin, an anti-mitotic metabolite of the roots of the may apple plant, *Podophyllum peltatam* (an old herbal remedy). Etoposide is a topoisomerase II inhibitor Etoposide was approved for lung cancer, choriocarcinoma, ovarian and testicular cancer, lymphoma, and acute myeloid

leukaemia. Teniposide was approved for tumours of the CNS, malignant lymphoma and bladder cancer.

Other compounds

The naphthoquinone pigment shikonin, a herbal medicine remedy, is produced by cell culture of *Lithospermum erythrorhizon*, mainly for cosmetic use. Unexpectedly, shikonin and two derivatives were found to inhibit tumour growth in mice bearing Lewis Lung carcinoma. Other plant natural products such as the isoflavone genistine, indole-3-carbinol (I3C), 3,3′- diindolemethane, curcumin (-) -epigallocatechin-3-gallate, resveratrol and lycopene are known to inhibit the growth of cancer cells. These natural compounds appear to act by interference in multiple cellular signalling pathways, activating cell death signals, and bringing on apoptosis of cancer cells without negatively affecting normal cells.

Marine anti-tumour products

Four marine anti-cancer drugs are already approved: cytarabine for leukemia, eribulin mesylate (Halaven®), for metastatic breast cancer, brentuximab vedotin (Adcetris® for anaplastic large T-cell malignant lymphoma, and Hodgkin's lymphoma, and trabectidine (Yondelis®) for soft tissue sarcoma and ovarian cancer.

Additionally, a number of marine-derived substances with potent anti-cancer properties are currently in clinical trials; phase III: plinabulin, plitidepsin, glembatumumab vedotin, and lurbinectedin; phase II: depatuxizumab mafodotin, AGS-16C3F, polatuzumab vedotin, PM184, tisotumab vedotin, and enfortumab vedotin; phase I: GSK2857916, ABBV-085, ABBV-399, ABBV-221, ASG-67E, ASG-15ME, bryostatin, marizomib, and SGN-LIV1A.

In 2007, the marine alkaloid trabectedin (Yondelis) was approved by FDA; a semisynthetic tetrahydroisoquinoline alkaloid originally derived from the marine tunicate Ecteinascidia turbinata, was the first marine anti-cancer agent approved in the European Union for patients with soft tissue sarcoma.

Another anti-tumour compound, aplidine, a cyclic peptide, has orphan drug status in Europe for acute lymphocytic leukaemia and is in Phase II clinical trials in the USA. Ecteinascidin 743 (ET 743) is in Phase III trials against sarcoma.

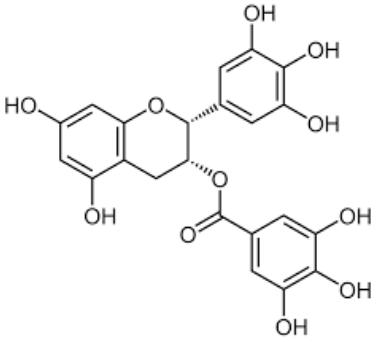
A major problem is that less than 1% of the commensal microbiotic consorta of marine invertebrates are culturable at this time. Curacin A, obtained from a marine cyanobacterium *Lyngbya majuscula* isolated in Curacao, showed potent anti-tumour activity. Other anti-tumour agents derived from marine sources include eleutherobin, discodermolide, bryostatins, dolastatins and cephalostatins.

Variants of the toxic dolastin from the sea hare *Dolabella auricalaria* seem promising against cancer. These include soblidofin (T2F 1027), which completed phase II against soft tissue sarcoma, and synthadotin (tasidotin, 1LX 651), which is at the same clinical stage against melanoma, prostate and non-small cell lung cancers. These are thought to be produced by cyanobacteria sequestered by the marine invertebrates in their diet.

The new actinomycete genus *Salinispora* and its two species, *S. tropica* and *S. arenicola*, have been isolated around the world. These require seawater for growth. *Salinispora tropica* makes a new bicyclic g-lactone b-lactam called salinosporamide A, which is a proteasome inhibitor in phase II clinical trials against multiple myeloma and mantle cell lymphoma. Also the genus *Marinophilus* contains species that produce novel polyenes, which have no anti-fungal activity but display potent anti-tumour activity.

Sources:
Microbial Biotechnology (2011) **4**(6), 687–699
Wikepedia
Mar Drugs. 2018 Feb; 16(2): 41.

Green tea compound could fight super bugs



Antibiotic resistant bacteria are one of the biggest threats to global health. Antibiotics have proven essential for treating bacterial infections since they were first used in the 1930s. However, bacteria are rapidly becoming resistant to the drugs designed to kill them. In the United States alone, drug resistant bacteria infect at least 2 million people each year, leading to about 23,000 deaths, according to the Centers for Disease Control and Resistance (CDC). As antibiotic resistant pathogens become increasingly prevalent, researchers are leaving no stone unturned in their search for innovative interventions.

The WHO warn that taking antibiotics when they are not needed - both by humans and livestock - speeds up multidrug resistance and puts everyone at risk. It is important to emphasise that it is not a person who becomes resistant, but the bacterium. This means that cures for common infections are under threat.

As researchers scramble to find solutions, a recent study concluded that a compound found in green tea might boost existing drugs; one particular compound, epigallocatechin, might bolster failing antibiotics and help them to kill bacteria more efficiently.

Researchers from the University of Surrey in the UK, focused on the bacterium *Pseudomonas aeruginosa* which can cause severe infections to the skin, the blood, and the respiratory and urinary tracts. The bacteria are becoming resistant to many antibiotics. Currently, *P. aeruginosa* infections are treated with a combination of antibiotics.

Researchers have been interested in epigallocatechin for a number of reasons. For instance, some studies have investigated possibilities that it might treat inflammation and rheumatoid arthritis. In the latest investigation, the researchers performed checkerboard and time–kill kinetic assays to assess synergy *in vitro*; the efficacy of the combination *in vivo* was tested using *Galleria mellonella* model of infection.

To gain insight into the mechanism of action accumulation assays were performed. They combined EGCG with aztreonam, which is an antibiotic commonly used to fight P. aeruginosa. They found that the combination reduced the numbers of clinical multidrug resistant strains of P. aeruginosa in laboratory cultures. The research investigated the interaction between EGCG and aztreonam in an animal model. Specifically, they used greater wax moth larvae, found to be a useful model for studying antibiotics. When they combined EGCG with aztreonam, it was more effective than using the drug or EGCG alone. They believe that EGCG increases the bacterium's permeability, allowing antibiotics to pass through more easily.

Combination of natural products, such as EGCG, with currently licensed antibiotics, may be a way of improving their effectiveness, and clinically useful lifespan.

Sources:

1. www.medicalnewstoday.com/articles/326561.php#1
2. Betts JW et al. J Med Microbiol. 2019. 68;10

How has clinical research fared in 2019?

Our diets influence our health

In 2019, the topic of how food choices influence our health has remained popular among researchers. One intriguing study, in Nature Metabolism in May, pointed out that protein shakes, which are popular among individuals who want to build muscle mass, may be a threat to health. Fitness protein powders, the study authors explain, contain mostly whey proteins, which have high levels of the essential amino acids leucine, valine, and isoleucine.

The research, in mice, suggested that a high intake of these amino acids led to overly low levels

of serotonin in the brain, a key hormone that plays a central role in mood regulation, but which is also implicated in various metabolic processes. In mice, the heightened levels of leucine, valine, and isoleucine, which caused excessively low serotonin, led to obesity and a shorter life span.

So, if too much of certain types of protein can have such detrimental effects on health, what about fiber? Dietary fiber, present in fruit, vegetables, and legumes, is important in helping the body take up sugars little by little. But how much fiber should we consume? This is the question addressed in a study commissioned by the WHO, and appearing in The Lancet in January. The research took into account the findings of 185 observational studies and 58 clinical trials, covering almost 40 years. It concluded that to lower their death risk, as well as the incidence of coronary heart disease, stroke, type 2 diabetes, and colon cancer, a person should ideally consume 25–29 g of fiber per day. Fiber-rich whole foods that require chewing and retain much of their structure in the gut increase satiety and help weight control and can favourably influence lipid and glucose levels.

On the other hand, several studies from this year draw attention to just how detrimental foods that are not 100% natural can be. A small trial, whose results came out in Cell Metabolism in May, showed that processed food leads to abrupt weight gain. The researchers blame this on the speed with which individuals end up eating processed foods, in particular. If one is eating very quickly, perhaps the gastrointestinal tract does not get enough time to signal to your brain that you're full. When this happens, one might easily over-eat.

And more research in mice, from Scientific Reports in January, found that emusifiers, which are a common additive present in many products from mayonnaise to butter, could affect gut bacteria, leading to systemic inflammation.

Cardiovascular health

Many studies this year have also been concerned with cardiovascular health, re-visiting long held notions and holding them up to further scrutiny. For instance, a study, in the New England Journal of Medicine in July, which involved around 1.3 million people suggested that when it comes to predicting the state of a person's heart health, both blood pressure numbers are equally important.

Blood pressure assesses two different values. One is systolic blood pressure, which refers to the pressure the contracting heart puts on the arteries when it pumps blood to the rest of the body. The other is diastolic blood pressure, which refers to the pressure between heartbeats. So far, only elevated systolic blood pressure is taken into account as a risk factor for cardiovascular disease. However, the new study concluded that elevated systolic and diastolic blood pressure are both indicators of cardiovascular problems. Its authors emphasise that the large amount of data supports this notion.

When it comes to protecting heart health, 2019 studies have shown that diet likely plays an important role. Thus, research in the Journal of the American Heart Association in August, showed that people who adhered to plant-based diets had a 32% lower risk of death that researchers associate with cardiovascular disease than those who did not. People who ate plant-based foods also had a 25% lower risk of all-cause mortality, according to this study.

And another study, from April in the journal Nutrients, warned that people who follow a ketogenic diet, which is high in fats and low in carbohydrates, and who decide to take a day off from this commitment every now and again, may experience blood vessel damage.

Medications: Friend or foe?

Medication is meant to help fight off disease, and improve physical or mental well-being. But most drugs can sometimes cause side effects.

For instance, in March, 2019 experts affiliated with the European Resuscitation Council, whose goal is to find the best ways to prevent and respond to cardiac arrest, found that a conventional drug

used to treat hypertension and angina, may actually increase risk of cardiac arrest.

By analysing the data of more than 60,000 people, the researchers saw that a drug called nifedipine, which is often prescribed for cardiovascular problems, appeared to increase the risk of sudden cardiac arrest. So far, healthcare practitioners have considered nifedipine to be perfectly safe. The current findings, however, suggest that doctors may want to consider offering people an alternative.

Another study, appearing in JAMA Internal Medicine in June, found that anti-cholinergic drugs, which work by regulating muscle contraction and relaxation, may increase a person's risk of developing dementia. People may have to take anti-cholinergics if some of their muscles are not working correctly, such as bladder or gastrointestinal conditions.

The research looked at the data of 58,769 people with and 225,574 people without dementia. It showed that older individuals, at least 55 years old, who were frequent users of anti-cholinergics were almost 50% more likely to develop dementia than those who had never used anticholinergics.

But, while common drugs that have been prescribed for years may come with hidden dangers, they are at least subject to trials and drug review initiatives. The same is not true for many other so-called health products that are readily available to consumers. Such findings highlight the importance of carrying out regular medication reviews.

Sources:
Medicalnewstoday.
www.medicalnewstoday.com/articles/327372.php#1

News from the FDA

FDA breakthrough therapy criteria

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

For purposes of Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy
- A drug that receives Breakthrough Therapy designation is eligible for the following:
- All Fast Track designation features
- Intensive guidance on an efficient drug development program, beginning as early as Phase 1
- Organisational commitment involving senior managers

Breakthrough Therapy designation is requested by the drug company. If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for Breakthrough Therapy designation and (2) the remaining drug development program can benefit from the

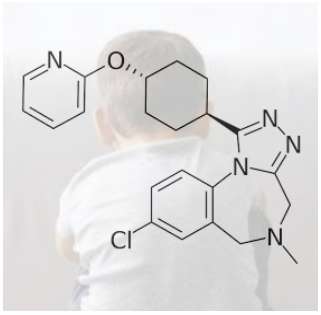
designation.

Ideally, a Breakthrough Therapy designation request should be received by FDA no later than the end-of-phase-2 meetings if any of the features of the designation are to be obtained. Because the primary intent of Breakthrough Therapy designation is to develop evidence needed to support approval as efficiently as possible, FDA does not anticipate that Breakthrough Therapy designation requests will be made after the submission of an original BLA or NDA or a supplement. FDA will respond to Breakthrough Therapy designation requests within sixty days of receipt of the request.

Source:
www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy

Drugs achieving FDA breakthrough status

Roche's autism drug scores FDA breakthrough status. Balovaptan could become the first drug to treat autism spectrum disorder



A drug that may improve social interaction and communication in people with autism spectrum disorder (ASD) has been granted Breakthrough Therapy Designation. Roche's oral investigational medicine Balovaptan could become the first drug approved for the disorder, and if it does it would mark a very big win for the Swiss pharma giant.

The FDA's designation bucks the regulator's usual trend of awarding Breakthrough Therapy Designations to oncology candidates. Roche's neuroscience drug met the FDA requirements mostly based on efficacy findings from the VANILLA study, a phase II trial of balovaptan in adults with ASD.

Novartis drug Promacta won another breakthrough status, setting up the Swiss pharma firm for a promising start to 2018.

The news comes hot on the heels of FDA breakthrough status for the company's breast cancer drug Kisqali. For rare blood disorder drug Promacta (eltrombopag), the status was awarded for its use in combination with standard immunosuppressive therapy for the treatment of patients with severe aplastic anaemia (SAA) as a first-line therapy.

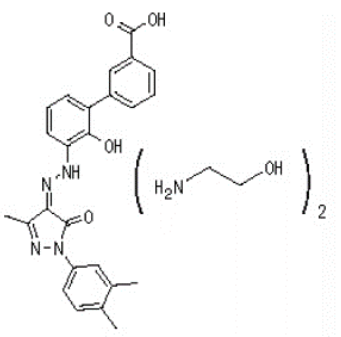
The head of Novartis oncology global drug development claims Promacta as a "promising medicine that, if approved for first-line use in SAA, may redefine the standard of care for patients with this rare and serious bone marrow condition".

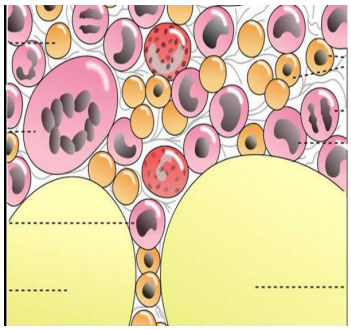
Known as Revolade in most countries outside the US, Promacta gained its breakthrough therapy designation following positive data, with 52% of treatment-naïve severe aplastic anaemia (SAA) patients achieved complete response with the drug given with standard immunosuppressive therapy.

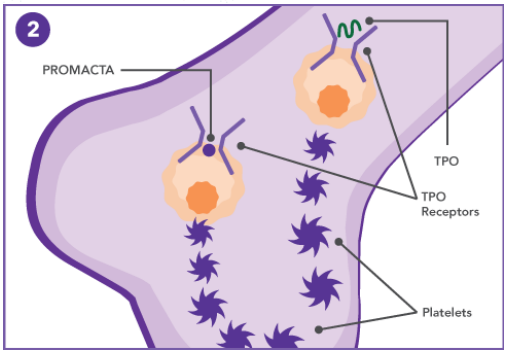
The drug, which is the only TPO receptor agonist indicated for SAA in the refractory setting, is already approved as a second-line therapy in the same indication.

Patients are diagnosed with SAA when their bone marrow fails to produce enough red blood cells, white blood cells and platelets and according to Novartis up to one-third of patients do not respond to current therapies of relapse.

Regulatory filings for a first-line indication in the US and Europe are expected to be made for Promacta/Revolade later this year.







Recent FDA Approvals

Abrilada (adalimumab-afzb) Injection
Treatment for: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease -- Maintenance, Ulcerative Colitis, Plaque Psoriasis

Amzeeq (minocycline) Topical Foam - Foamix Pharmaceuticals
Treatment for: Acne

Avsola (infliximab-axxq) - Amgen Inc
Treatment for: Crohn's Disease,Maintenance, Ulcerative Colitis, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis

Biorphen (phenylephrine hydrochloride) Injection Eton Pharmaceuticals, Inc
Treatment for: Hypotension

Fetroja (cefiderocol) Injection -Shionogi Inc
Treatment for: Complicated Urinary Tract I infections

Gvoke (glucagon) Ready-to-Use Injection - Xeris Pharmaceuticals, Inc
Treatment for: Hypoglycemia

Ibsrela (tenapanor) Tablets - Ardelyx, Inc
Treatment for: Irritable Bowel Syndrome

Oxbryta (voxelotor) Tablets - Global Blood Therapeutics, Inc
Treatment for: Sickle Cell Anemia

RediTrex (methotrexate) Injection - Cumberland Pharmaceuticals Inc
Treatment for: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriasis

Reyvow (lasmiditan) Tablets - Eli Lilly
Treatment for: Migraine

Rybelsus (semaglutide) Tablets - Novo Nordisk
Treatment for: Diabetes Type 2

Secuado (asenapine) Transdermal System - Noven Pharmaceuticals, Inc
Treatment for: Schizophrenia

Talicia (amoxicillin, omeprazole and rifabutin) Delayed-release capsules - RedHill Biopharma Ltd
Treatment for: Helicobacter pylori Infection
Treatment for: Partial-Onset Seizures in adults.
Treatment for: Neutropenia Associated with Chemotherapy

Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) Tablets - Vertex Pharmaceuticals Inc
Treatment for: Cystic Fibrosis

Vumerity (diroximel fumarate) Delayed-Release Capsules - Biogen
Treatment for: Multiple Sclerosis

Xcopri (cenobamate) Tablets - SK Life Science, Inc
Treatment for: Seizures

Ziextenzo (pegfilgrastim-bmez) Injection - Sandoz

Answers to: Test your knowledge

Correct answers:
1-C; 2-A; 3-D

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH or FDA. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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