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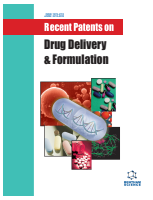
REVIEW ARTICLE

Scientific Papers and Patents on Substances with Unproven Effects. Part 2



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Abstract: Several examples are discussed in this review, where substances without proven effects were proposed for practical use within the scope of evidence-based medicines. The following is discussed here: generalizations of the hormesis concept and its use in support of homeopathy; phytoestrogens and soy products potentially having feminizing effects; glycosaminoglycans for the treatment of osteoarthritis and possibilities of their replacement by diet modifications; flavonoids recommended for the treatment of chronic venous insufficiency and varicose veins; acetylcysteine as a mucolytic agent and its questionable efficiency especially by an oral intake; stem cells and cell therapies. In conclusion, placebo therapies can be beneficial and ethically justifiable but it is not a sufficient reason to publish biased information. Importantly, placebo must be devoid of adverse effects, otherwise, it is named pseudo-placebo. Therapeutic methods with unproven effects should be tested in high-quality research shielded from the funding bias. Some issues discussed in this review are not entirely clear, and the arguments provided here can initiate a constructive discussion.

Keywords: Placebo, hormesis, nutrition, phytoestrogens, soy, osteoarthritis, acetylcysteine.

1. INTRODUCTION

This paper is a continuation of the previously published article [1]. Analogously to the preceding review, the PubMed, Cochrane and other databases were searched for relevant articles reporting trials as well as reviews and meta-analyses. More articles came to the attention through other means *e.g.* reference lists. It is evident for a reviewer of scientific literature that the quality of argumentation in some areas of medical and biological research deteriorated since last decades. Another tendency is that substances without proven effects and questionable treatments have been advertized, corresponding products being marketed in the guise of evidence-based medications. Scientific publications are required to register drugs and treatments to obtain permissions for the practical use; accordingly, such publications appeared, sometimes being evidently biased. Patients can be influenced not only by the advertizing but also by unobjective professional publications. In Russia, the marketing of placebos under the guise of evidence-based medications is quite usual [1]. Several examples are discussed in this review, where drugs and dietary supplements with unproven effects and unclear action mechanisms are directly or indirectly presented as evidence-based medications. It was not the aim of this article to provide a comprehensive review of substances under discussion; there are many reviews that are cited here. The conclusions of this paper are partly based on theoretic considerations. As mentioned above, the problem is a difficulty of distinguishing between reliable and unreliable reports due to declared or non-declared conflicts of interest. In such circumstances, theoretic considerations gain importance.

Not only questionable data have been published but also theoretic concepts used beyond their areas of applicability. An example is hormesis - a concept of biphasic dose-response to various pharmacological and toxicological stimuli; typically, low-dose exposures induce a beneficial response while higher doses cause toxicity [2]. Theoretically, hormesis as a general principle is conceivable only for factors that are present in the natural environment, having induced an evolutionary adaptation, so that a deviation in either direction from an optimum would be unfavorable [2-4]. There are no reasons to expect hormetic (biphasic) dose-responses a priori for factors that are not present in the natural environment. All clinically significant effects, hormetic or not, must be tested according to the principles of evidence-based medicine. Some pharmacological agents can exert cumulative effects or act synergistically with other noxious factors *e.g.* on cells with a limited or absent capability of mitosis such as cardiomyocytes or neurons. It can be of particular importance in conditions when such cells are predamaged *e.g.* by ischemia so that even a small additional impact would act according to a no-threshold pattern without hormesis. Under such circumstances, which are not uncommon especially in gerontology, the concept of hormesis can

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be unsafe if used in the clinical decision-making [5]. For example, it would hardly be indicated to consume small amounts of ethanol, a known hormetic agent, by a patient with hepatic failure. At the same time, certain publications present hormesis as a general biological principle [6-8]. Such papers can be cited in support of homeopathy, placebo and pseudo-placebo, in gerontology and other fields of medicine. A placebo must be devoid of unfavorable effects; otherwise, it is called pseudo-placebo [9].

Homeopathy claims a curative action for small drug doses, of which high doses would cause symptoms similar to those the patient has. Suggestions that homeopathy is based on hormesis create an illusion that it employs a scientific principle. Homeopathy has never been grounded on scientific evidence [10]. Nevertheless, homeopathic medications have been proposed, patented and used in diverse diseases *e.g*. tuberculosis, acute pneumonia, viral infections or myopia (RU2203674C1, RU2063224C1, RU2119338C1, RU2192888C1) [11-14]. In particular, it is precarious when homeopathic medications are delivered by invasive methods *e.g*. intraarticular injections (RU2015147929A) [15]. Empirical knowledge accumulated by homeopathy and folk medicine should be tested by scientific methods.

2. FOCUSED REVIEW

2.1. Phytoestrogens and Soy Products

Phytoestrogens (PhE) are plant-derived substances with structural similarity with estradiol [16, 17]. The most extensively studied PhE are isoflavones and coumestans. Isoflavones are most abundant in soy. Some other plants also contain PhE, in particular, red clover. The consumption of PhE and soy foods has been associated with health benefits; however, adverse effects on the reproductive and endocrine system seem to be undervalued [16]. Some epidemiological studies suggest that dietary intake of PhE contributes to a decreased incidence of postmenopausal cardiovascular and thromboembolic events [18]. In the same review, it was acknowledged that trials on PhE had been limited in many aspects including the number of participants enrolled, clinical endpoints investigated, and lack of long-term follow-up [18]. Furthermore, PhE were reported to be significantly more effective than placebo in reducing the frequency and severity of hot flashes [19]. However, the evidence from observational studies and randomized trials was generally lacking [20, 21]. According to several reviews, there are no reliable arguments in favor of PhE effectiveness against menopausal symptoms so that current evidence does not generally support their use [22-24]. The efficacy of PhE against vasomotor symptoms has failed the test of randomized clinical trials, whereas the efficacy of PhE on menopausal vasomotor symptoms was found to be similar to that of placebo [25, 26]. Definite conclusions on possible beneficial effects of PhE could not be made [17]. According to a Cochrane review, there is no conclusive evidence that PhE reduce the frequency or severity of hot flushes and night sweats in peri- and postmenopausal women, while many of the trials were small, of short duration and poor quality. Bedsides, publication bias favored papers with positive results [27].

The analysis of earlier findings from enrichment, the diet with soy protein has failed to confirm beneficial cardiovascular effects by way of lipid-lowering, vasodilatation or lipoprotein oxidation [28]. In particular, there is little evidence in favor of the prevention of menopausal osteoporosis [17, 29-32]. Admittedly, the matter is controversial and positive effects of PhE have been reported [33, 34]. For example, the following statement from a favorable report appears questionable: "Comparative assessment showed no significant differences between the effectiveness of the hormone therapy and the PhE used in the study, in terms of effects on bone mineral density and bone resorption" [34], because the hormonal activity of PhE is known to be much lower than that of estradiol and NETA (norethisterone acetate) used in this study [34]. According to the European Food Safety Authority (EFSA), existing evidence does not suffice to establish a relationship between the maintenance of bone mineral density and the consumption of soy isoflavones [17]. The use of PhE is not advocated also because of conflicting data about safety [35]. There have been reports on adverse effects and interactions with other medications [36]. Moreover, soy is one of the most allergenic foods, so that some people must avoid it [17, 37]. The conventional menopausal hormone therapy remains the only treatment that is consistently more effective than placebo in controlled trials [38]. The majority of high-quality studies demonstrated no clear benefit and some potential for harm, thus further research is necessary to formulate recommendations [38].

The theoretical basis for the use of PhE in the menopause appears doubtful. Biological effects of estrogens are mediated by receptors. It is unclear, why accidental plant-derived analogs must be used instead of natural or synthetic hormones that are complementary to the receptors. Some commercial PhE preparations contain a mixture of ingredients of obscure origin having unpredictable effects [39]. The vision of PhE as a natural and safe alternative to estrogens [25] is unfounded: these substances are in fact less natural for humans than hormones. Moreover, the use of soy as animal fodder can result in the accumulation of PhE and their active metabolites such as equol in meat and other animal products. Equol has a relatively high estrogenic potential, it is produced by intestinal bacteria in farm animals and fowl [40, 41].

Adverse effects associated with the intake of soy have been reviewed [16, 42-44]. Derangements of the reproductive health and feminizing effects in men are regarded to be rare and mild [42] but may be statistically detectable in large populations. It was reported on dysmenorrhea in women, mild change of gender roles in girls and gynecomastia in a man consuming soy products [16, 45, 46]. A cross-sectional study of 11,688 women showed that abundant intake of isoflavones was associated with an increased risk of lifetime nulliparity and nulligravidity [47]. Hormonal effects of PhE may lead to fertility problems possibly due to an impact on the menstrual cycle, oocyte quality and endometrial receptivity [43]. An association between soy exposure and early menarche was reported [48]. Experimental data demonstrate that soy isoflavones, also at doses and concentrations observable in humans including infants, can influence neuroendocrine pathways in animals of both sexes. Relevant doses of PhE have an impact on the differentiation of ovaries and

fertility in animals [16, 49, 50]. Alterations of male sexual development and deficits of sexual behavior were noticed in rats and rabbits [51, 52]. Moreover, some PhE *e.g*. genistein can exert androgenic effects [53], which is not surprising as PhE are plant substances with accidental similarity to human hormones, so that their effects are a priori unpredictable. It was suggested that PhE are estrogen receptor modulators thus being different from estrogens [54]. It is questionable, however, whether such modulations, also called endocrine-disrupting [16, 55], are favorable for soy consumers, especially at a young age. Perinatal period, infancy, childhood and puberty are critical periods during which maturing systems are particularly sensitive to hormonal disruptions [55]. As global consumption increases, greater awareness and consideration of the endocrine-disrupting properties of soya by nutrition specialists and other health practitioners are needed. Parents should be aware of possible estrogenic effects if they choose to feed their infants with soy-based formulas [16]. Finally, soy-based emulsions are known as causative factors of cholestasis related to pediatric parenteral nutrition [56].

Another contradiction was encountered in the literature: it was stated that "findings from a recently published metaanalysis and subsequently published studies show that neither isoflavone supplements nor isoflavone-rich soy influences total or free testosterone levels. Similarly, there is essentially no evidence from the nine identified clinical studies that isoflavone exposure affects circulating estrogen levels in men" [57]. In a case report on gynecomastia associated with soy consumption by a man it was noted: "After he discontinued drinking soy milk … his estradiol concentration slowly returned to normal" [46]. Statements of this kind are potentially misleading because PhE, being estrogen analogs, exert hormonal effects on their own, not necessarily influencing concentrations of endogenous hormones.

This paper was not intended to be a review on PhE: there have been comprehensive reviews that are cited here. The main purpose was to convey the following ideas: (1) PhE are used for compensation of estrogen deficiency in menopause; however, their estrogenic potential does not prevent from the use of soy in infant formulas and other foodstuffs. As mentioned above, the feminizing effect of soy products may be subtle, detectable only statistically in large populations. This matter should be clarified by independent research. (2) There is a tendency of placebo marketing in the guise of evidence-based medications. The published criticism is sometimes disregarded. For example, the supposed anti-atherogenic action of certain PhE was corroborated by experiments with cell cultures. In these experiments, the ability of serum to induce accumulation of cholesterol in cultured cells was interpreted as an indicator of atherogenicity [1, 58, 59]. The reliability of these experiments has been questioned; however, the publication series has been continued without references to the published criticism [60, 61]. In the Russian-language literature, PhE are promoted by misquoting of foreign literature; examples are shown in a study [60]. Scientifically questionable methods and theories are sometimes used for the official registration and patenting of drugs, dietary supplements and treatment methods *e.g*. (RU 2471485C1) [59, 62]. As a result, substances with unproven effects are recommended to patients, who may be misinformed not only by the advertising but also by some publications supposed to be scientific.

2.2. Glycosaminoglycans for the Treatment of Osteoarthritis

Chondroitin (Ch) is a glycosaminoglycan and Glucosamine (Ga) is an aminosaccharide acting as a substrate for the biosynthesis of glycosaminoglycans. Ch undergoes hydrolysis in the intestine; administered orally, it may act as a source of precursors for glycosaminoglycans. Hyaluronic Acid (HA) is a glycosaminoglycan used for intra-articular injections. These substances are named chondroprotectives and are used for the treatment of osteoarthritis. The oral preparations have been apprehended as Symptomatic Slow-Acting Drugs in Osteoarthritis (SYSADOA) [63]. This term seems to be suboptimal: oral glycosaminoglycans and their precursors are not symptomatic in the narrower sense because they are aimed primarily not to alleviate symptoms but to compensate for a supposed deficiency of cartilage precursors. The evidence is controversial, effectiveness being largely due to the placebo effect [64]. Many studies have been sponsored by the industry. There is skepticism in the scientific community [65]. A meta-analysis concluded that "Ch, Ga, and their combination do not have a clinically relevant effect on perceived joint pain or on joint space narrowing" [66]. According to a Cochrane review, trials of the mostly low-quality report that Ch alone or in combination with Ga was better than placebo for the pain relief in participants with osteoarthritis in short-term studies [67]. The most recent meta-analysis suggested that HA monoinjections produce results similar to multi-injections in terms of pain relief in the treatment of knee osteoarthritis, although bias and placebo-effect were not completely excluded [68]. It is known that pain measurements in clinical trials are difficult, possibly contributing to the exaggeration of treatment effects. Pain, stiffness and other studied endpoints are largely subjective, which means that a great part of the treatment successes can be attributed to the placebo effect [69-72]. There are many studies and reviews reporting the efficiency of chondroprotective drugs compared to placebo, but reliability is often questionable due to declared or non-declared conflicts of interest. Quality of research and possible influence by the industry must be taken into account defining inclusion criteria for studies in meta-analyses and reviews.

The theoretical basis of the supposed chondroprotection is unclear. Glycosaminoglycans and their precursors are not irreplaceable; they are produced by the body also in vegetarians, who consume no immediate precursors. It appears doubtful that oral supplementation of Ch and Ga can shift the balance between cartilage synthesis and degradation in the whole body so that it would be significant for joints. Furthermore, the sources such as shellfish chitin and fungi for Ga, cartilage from mammals, birds or fish for Ch as well as contaminants may impart undesirable properties to the preparations [73, 74].

In regard to the intra-articular injections of HA, a meta-analysis concluded that "currently available evidence suggests that intra-articular HA is not clinically effective and may be associated with increased risk of adverse events" [75]. Another meta-analysis and systematic review con-

cluded that in patients with knee osteoarthritis, intra-articular HA is associated with a small, clinically irrelevant benefit and an increased risk of adverse events [69, 76]. The evidence remains inconsistent and controversial [77]. According to a Cochrane review on HA for ankle osteoarthritis, it is unclear if there is a benefit or harm from HA compared to placebo. Inconclusive results were also obtained comparing HA to other treatments [78].

The action mechanisms of intra-articular HA are hardly understandable including viscosupplementation or lubrication of joint surfaces [79]. Viscosity changes after HA injections can be measured *e.g*. adding HA to cadaverous synovial fluid or approximately calculated, knowing the viscosity of the synovial fluid, of injected solution, and corresponding volumes. Both pre- and post-treatment viscosity was found to be within the range of normal values [80]. In any case, the lubrication effect cannot last long. No explanation has been found for the discrepancy between the short intra-articular half-life of injected lubricant and the reported duration of the carry-over effect. The rheological effect of exogenous HA in the articular cavity probably lasts <1 day [81]. The intra-articular half-life of Hyalgan (sodium hyaluronate) is about 17 hours; the low molecular weight component of Synvisc (Hylan G-F 20 constituting about 90% of the preparation) has a half-life of 1.5 days; the minor component with a higher molecular weight -8.8 days [80]. By contrast, the carry-over effect after the treatment cessation lasted from 3 months with oral chondroprotective to 6-9 months with intra-articular injections [82]. The half-life of an HA preparation with artificial cross-linking was reportedly up to 4 weeks [83]; but again, there are no reasons to expect a much longer carry-over effect. A short-term functional improvement due to the viscosupplementation may reinforce the placebo effect by the mechanism of conditioning. It is known that some invasive procedures have a pronounced placebo effect. As mentioned above, a placebo must be devoid of adverse effects; otherwise, it is called pseudo-placebo [9]. In particular, the intra-articular therapy of hip osteoarthritis is associated with adverse events due to the proximity of important anatomical structures (RU2396961C1) [84, 85].

HA is a polymer; according to the law of mass action, its local enrichment would displace the chemical equilibrium toward low-molecular precursors *i.e*. reduction of viscosity. Therefore, suppositions about enhanced biosynthesis of endogenous HA after injections of the same substance [63, 86] seem to be groundless. As for molecular mechanisms studied *in vitro*, their clinical relevance is questionable, among others, because of higher concentrations of tested substances *in vitro* than *in vivo*. Of note, Ch, Ga and HA have primarily been chosen for supplementation, so that a probability of their specific anti-inflammatory action, inhibition of chondrodegenerative enzymes or pain mediators [86-88] is a priori the same as for substances taken at random.

In Russia, Ch, Ga and HA are named as chondroprotectors. These drugs are prescribed to osteoarthritis patients including elderly people with low incomes. Many patients purchase the drugs for a prolonged use [89]. Chondroprotector-containing ointments and preparations for intra-articular injections have been patented (RU2396961C1, RU2376011C1) [84, 90]. In the author's opinion, it would be more or less equivalent to recommend to osteoarthritis patients a diet rich in natural glycosaminoglycans: animal joints, chicken wings *etc*. This idea is not new, it was discussed at conferences. To support the placebo effect, patients can be advised that such diet would saturate their organism with precursors of cartilage similarly to the pharmaceuticals. In this connection, it might be informative to study the prevalence of osteoarthritis in vegetarians. Effectiveness of a dietary supplementation of natural glycosaminoglycans compared to Ch and Ga preparations can be tested *e.g*. in dogs with osteoarthritis, giving them food rich in cartilage. A recent review concluded that benefits from Ga and Ch in canine osteoarthritis can neither be confirmed nor denied. Unfortunately, not only human but also animal studies are at risk of funding bias [91].

2.3. Flavonoids as Venoactive Drugs

Certain Flavonoids (Fl) are used for the treatment of chronic venous insufficiency and varicose veins. In the past, some supposedly venoactive Fl (rutin, escin, quercetin) were produced from medicinal plants. Today, the Micronized Purified Flavonoid Fraction (MPFF) consisting of 90% diosmin and 10% hesperidin is broadly used [92]. Diosmin is synthesized from hesperidin extracted from oranges [93]. In the United States, preparations of Fl are classified as dietary supplements and in some European countries - as drugs, which does not necessarily mean an extensive use. In Scandinavia, drugs are rarely prescribed for the chronic venous disease [94, 95]. In Spain, for certain phlebotonics (calcium dobesilate, chromocarbe and naftazone) the indication for use in chronic venous insufficiency has been withdrawn, while for some other ones (aminaftone, diosmine, hidrosmine, escin and some rutosides), the conditions of use during exacerbations of chronic venous insufficiency have been limited to 2-3 months [96].

The following effects of venoactive Fl have been discussed: phlebotonic, anti-edematous, anti-inflammatory and anti-oxidative. The action mechanisms are not well understood [93, 96, 97]. Smooth muscles of larger veins have no noticeable tone and do not relax under the influence of vasodilators [98]. Lumina of collapsed veins are slit-like, muscular bundles interchanging with fibrous tissue. In varicose veins and post-thrombotic syndrome, the veins are distended, smooth muscles being atrophic or replaced by connective tissue [99, 100]. This is against any significant venotonic effect of Fl; in particular, its durability is doubtful, which pertains also to a supposed potentiation of the norepinephrine action [93, 98, 100]. At the same time, quercetin was reported to inhibit norepinephrine-induced vascular contraction [100]. The vasoconstrictive effect of norepinephrine is transient; its blood concentration fluctuates *e.g*. in stress, whereas Fl are used in permanent conditions such as venous insufficiency and varicose veins. Moreover, a significant phlebotonic action seems to be improbable without a concomitant influence on the arteries. If Fl considerably enhanced the action of norepinephrine or otherwise caused vasoconstriction, they would elevate the blood pressure [101]. Although some degree of venous tone does exist [102, 103], there is no reliable evidence that the tone can be significantly influenced by Fl. On the other hand, if vasoconstriction is indeed favorable in vein diseases, known vaso-

constrictive agents could be used instead of Fl with their unproven efficiency.

Pharmacologic effects can be measured *e.g*. using isolated veins [103]. For example, dihydroquercetin did not modify the basal tone of isolated rat veins [104]. It was reported that diosmin heightens the sensitivity of smooth muscles from rat femoral veins to calcium, which might explain the phlebotonic action (the study was supported by manufacturers) [105]. On the contrary, hesperetin (the aglycone form of hesperidin) induced vasodilatation in humans and hypertensive rats [106, 107]. The vasorelaxing effect was demonstrated also for eriodictyol [107]. Overall, the quality of studies on this topic is regarded to be low, favorable effects being often exaggerated [97, 108]. The most rigorously conducted trial did not find any benefit from Fl in the treatment of venous leg ulcers [108]. Subjective improvements (pains, cramps, swelling sensation, heavy legs) are often noticed [93, 99, 109, 110], which may be caused by a placebo effect. Admittedly, an improvement of venous hemodynamics under the influence of MPFF was recorded by strain gauge plethysmography and ankle circumference measurements in patients with chronic venous insufficiency [92, 110-113]. The data on foot volumetry have been unconvincing [94, 114].

Mechanisms of supposed anti-inflammatory and anti-edematous effects of Fl are hardly comprehensible. Should anti-inflammatory or diuretic agents be indeed indicated, well-known drugs could be used instead of Fl with their unproven efficiency [111]. Furthermore, the anti-oxidative capacity of Fl has been discussed. Antioxidants are generally regarded to be far from the scientifically founded clinical application [1, 115, 116]. In any case, it is unclear why antioxidants should be used in conditions with tissue hypoxia such as venous insufficiency.

Adverse effects of Fl are reported to be mild to moderate across studies. The most common events are inflammatory skin lesions, gastrointestinal disturbances and arterial hypertension [96, 108]. In this connection, the biological role of Fl as repellents, protecting plants from herbivores, should be mentioned. Certain Fl are toxic for some insects and other organisms [117]. Presumably, Fl are weak toxins stimulating in some circumstances defense mechanisms of the host [118], so that their abundant intake may be associated with adverse effects especially in chronic disease or advanced age. Moreover, concentrations of Fl in drugs and nutritional supplements are higher than in a usual diet. Excessive amounts of polyphenols reaching the colon was reported to cause dysbiosis [119].

Despite the arguments discussed above, there are numerous papers reporting favorable effects of Fl in venous diseases [120]. Many studies were sponsored by the industry. Obviously, verification in large-scale independent experiments is needed. Should useful properties of Fl be confirmed, the question will arise whether pharmaceuticals can be replaced by enhanced consumption of citrus fruit as a source of Fl. Concentrations of different Fl in citrus juices are listed in [121]. Remarkably, some commercial juices contain more Fl than hand-pressed ones probably due to the forceful pressing and use of pulp. However, some commercial products in the former SU, labeled as citrus juices, are diluted, flavored and sweetened by syrup [122].

In conclusion, the evidence in favor of the phlebotonic action of Fl is inconsistent, potential mechanisms being hardly comprehensible theoretically. The effectiveness of venoactive drugs needs verification in large-scale studies protected from conflicts of interest, using objective methods such as measurements of supramolecular circumference, plethysmography, water volumetry and modern optoelectronic methods.

2.4. Acetylcysteine as a Mucolytic Drug

Acetylcysteine (N-acetyl-L-cysteine or NAC) is a mucolytic agent hydrolyzing disulfide bonds that link together mucin monomers. However, a clinically significant mucolytic effect is not well documented especially if the substance is taken per os [123, 124]. There is probably a placebo effect reinforced by Pavlovian conditioning if NAC had been administered together with expectorants or inhalations. The intravenous NAC was found to be ineffective in a placebo-controlled randomized study [125, 126]. It was pointed out that all positive findings of NAC in chronic obstructive pulmonary diseases originated from studies either investigating small numbers of cases or conducted in groups of patients not representative of wider populations [127]. The Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) showed that NAC is ineffective in preventing deterioration of lung functions among patients with Chronic Obstructive Pulmonary Disease (COPD) [128]. It was concluded that there had been no randomized controlled trials demonstrating a benefit from inhaled NAC in the treatment of airway diseases, while no data have convincingly demonstrated improvements of mucus expectoration [129-132]. At the same time, there is a risk of epithelial damage when NAC is administered as aerosol [132]. Inhaled NAC was found to be ineffective in atelectasis and mucus plugging in intubated patients; its effects in chronic lung disease were characterized as "unclear" [133, 134]. Inhaled aerosolized NAC was rapidly cleared from the lungs without changing the physical properties of sputum [135]. At the same time, a systematic review found that the treatment with mucolytics reduced the frequency of exacerbations in patients with COPD, whereas some studies applied NAC [136]. The latter findings were supported by a pharmaco-epidemiologic study [137], although bias was held possible [138]. The Cochrane and other reviews concluded that there is no evidence supporting the use of both oral and nebulized NAC for the routine treatment of cystic fibrosis [125, 130, 139]. In particular, NAC exerted no favorable effects on forced vital capacity, other important indices and the death rate in cystic fibrosis [139].

The following considerations cast doubt on the effectiveness of NAC as a mucolytic agent especially if taken per os. NAC was detected neither in airway secretions nor in bronchoalveolar lavage, while cysteine concentrations did not increase in the lavage fluid following an oral administration of NAC [124, 125, 132, 140, 141]. A slight increase in radioactivity of bronchial secretions after oral intake of ^{35}S-NAC does not prove that there was a chemically active substance in the bronchi [142]. A controlled double-blind study showed no significant differences in lung functions, mucocil-

iary clearance and sputum viscosity between oral NAC and placebo [125, 143]. This is not surprising as the oral bioavailability of NAC is low (4-10%), the substance being metabolized in the gut, liver and other tissues, ~30% of the clearance occurring through the kidneys [125, 132, 144].

A separate topic is the use of NAC for the treatment of microbial infections forming biofilms that play a role in the pathogenesis of inflammatory lesions in the upper respiratory tract, sinusitis, otitis and tonsillitis [145]. The antibiotic resistance of bacteria in biofilms contributes to the chronicity of inflammation [146]. Difficulties of biofilm eradication with systemic antibiotics have led to consider non-antibiotic therapies including NAC. It was reported that mucolytic activity of NAC contributes to the eradication of tonsilar biofilms [147, 148]. There is evidence that NAC interferes with the biofilm formation in the nose, throat and oral areas potentiating the action of antibiotics [149-152]. *In vitro* studies found that NAC at relatively high concentrations lowers sputum viscosity [153, 154]. Obviously, it is easier to achieve an efficient topical concentration in the nose, throat and oral areas than in the bronchi.

Apart from the mucolytic effect, NAC was supposed to possess antioxidative, anti-inflammatory and antimicrobial activity [152, 155-158]. The data on the anti-inflammatory action of NAC are limited, the mechanism is actually unclear. Suppositions about antimicrobial activity of NAC appear speculative; the matter should be clarified by microbiological methods. As mentioned above, synergism with antibiotics in biofilm eradication may be of clinical significance for the areas, where sufficient concentrations of NAC can be attained. Antioxidative effects have been discussed previously [115, 116]; in any case, they are not directly related to the supposed mucolytic activity of NAC.

In conclusion, there are reasons to doubt that NAC possesses any clinically significant mucolytic activity beyond the placebo effect, in particular, if taken per os. The matter can be clarified by the sputum viscosimetry using NAC concentrations comparable to those *in vivo*, by measurements of NAC concentrations in expectorated sputum from patients receiving the substance per os.

2.5. Stem Cells and Cell Therapies

Last time, numerous papers on Stem Cells (SC) have been published, some of them applying such terms as rejuvenation or anti-aging strategy [159, 160]. Discussed topics include the differentiation of exogenous SC into various cell lineages, replacement of senescent, dysfunctional and damaged cells. Of note, assumptions that the progeny of SC can differentiate into specialized cellular elements have not been confirmed for such a perfect SC as the fertilized ovum. In extrauterine pregnancy, no differentiation of embryonic cells towards surrounding tissues is observed but an embryo and germinal layers are formed, although a fertilized ovum and its progeny are totipotent SC, while blastocyst cells are pluripotent [161]. The implantation of embryonic SC can result in the development of teratoma [162]. It is known that a focal cell proliferation results in the formation of a nodule rather than engrafting of individual cells into surrounding tissues. For a pathologist, it is hard to envisage how SC migrate in tissues such as myocardium, liver or cartilage to the places where they are supposed to be needed and engraft in preexisting structures. In osteoarthritis, SC would have to move through a dense matrix of hyaline cartilage. If even SC are homing in defects of cartilage and synovial surfaces, proliferate there and produce extracellular substances, it remains unclear how the congruence of joint surfaces is preserved, why focal cell proliferation does not result in excrescences crumbling into the articular cavity causing dysfunction and inflammation. It was reported that SC disappear quickly after an intra-articular injection [163]. Reproducible protocols of chondrogenesis by SC do not exist [164]. The latest review did not recommend SC therapies for knee osteoarthritis for lack of high-quality evidence [165]. Admittedly, many papers report the efficiency and relative safety of cell therapies [166, 167], which is generally the case for substances with unproven effects discussed in this review. There are often no means to distinguish between reliable and unreliable publications *i.e.* to exclude bias.

Furthermore, in papers discussing the therapy of liver cirrhosis, a differentiation of exogenous SC to hepatocytes and stimulation of hepatocyte proliferation is regarded as possible [168, 169]. "The ability of mesenchymal SC to differentiate into hepatocyte-like cells makes them an ideal alternative method for treating liver fibrosis" [170]. However, the possibility of differentiation along the same mesodermal lineage to fibroblasts is not discussed. Such differentiation would possibly accelerate the progression of fibrosis and cirrhosis. Moreover, the theoretical basis for the cell therapy of liver cirrhosis is hardly comprehensible because hepatocytes are capable of mitosis and can hyperregenerate forming cirrhotic nodules.

In regard to cell therapies of neurodegenerative disease, doubts are persisting about the ability of SC to migrate to the target area and differentiate into neurons with correct synaptic connections [171, 172]. Some pre-clinical studies were, however, promising [171]. Two clinical trials demonstrated that SC therapies did not ameliorate symptoms of Parkinson's disease compared to dopaminergic medications; in addition, the patients exhibited graft-induced dyskinesia. A general shift in the goals of SC research from individual cell therapies to mechanistic studies of diseases has been noticed [173, 174]. Results of preclinical studies on SC therapy in Huntington's disease have been inconsistent [175]. In regard to Alzheimer's disease, promising results in animal models are deemed sufficient to initiate clinical trials; however, this area is notable for a poor translation to the clinic [173, 176]. One of the main challenges remains the risk of immune rejection [173].

In regard to cardiopulmonary diseases, SC-based therapies are still at their preliminary stage [177]. According to Cochrane reviews, there is insufficient evidence for a beneficial effect of cell therapies in patients with acute myocardial infarction. As for heart failure, low-quality evidence indicated that SC treatments may reduce mortality and improve left ventricular ejection fraction. However, bias due to lack of blinding, as well as reporting, publication and funding bias could not be ruled out completely [178, 179]. The poor engraftment and survival of implanted cells are a challenge [180-183]. In particular, the adipose-derived cell

therapy with cardiac or systemic administration had no clear clinical effectiveness but was associated with adverse events [184]. Since the early 2000s, several studies reported that SC transplants can regenerate the rodent heart after an experimental infarction. This experience was translated into the clinic. However, efficacy in human studies has been ambiguous or nil. It has become clear that SC fail to engraft and do not form new myocardium [183, 185]. Alternative action mechanisms have been proposed: immunomodulating, paracrine (anti-inflammatory, immunosuppressive, anti-apoptotic, anti-fibrotic, angiogenic, mitogenic) and activation of local precursor cells [160, 166, 186-188]. It was hypothesized that SC secrete anti-aging substances [189]. However, there are no reasons to expect from morphologically primitive SC or partly differentiated progenitors more specialized functions than from mature cells. Note that the biological mission of SC is mitosis rather than secretion of cytokines. In any case, experiments with mature cells or cell-free materials would be less expensive. Of note, cardioprotective and proangiogenic effects of cell-free supernatants of SC were reported [183]. The use of cell-free products allows a better dose standardizing than the cell transplantation [190].

Allogenic transplantations are accompanied by a risk of infections and immunologic adverse events. The immune system may recognize transplanted cells as foreign, launching an immune reaction [161, 191]. In cardiology, routes of cell transplantation include intravenous, transendocardial, intracoronary and transepicardial injections [192-195]. In this connection, sources of the cell material for intracoronary injections *e.g.* abortion specimens and their purification from immunogenic components are essential [193], commented previously [196, 197]. Infusions of autologous bone marrow cells or fractions of the patient's own blood are sometimes called autotransplantation; obviously, it is associated with lower risks than allogeneic transplantation. However, benefits from such procedures are questionable apart from a restoration of the pool of hemopoietic cells after a cytotoxic therapy, which has been applied long since. Numerous CT treatments have been patented; for example cells from human placentas were injected into acupuncture points as a "method of treatment of ischemic angiopathy of lower extremity vessels" (RU2649498C1) [198].

For all that, SC is a promising field of research. Studies of differentiated cells and cell-free products mimicking paracrine effects of cell therapies are promising as well. There is an opinion that SC therapies with scant evidence of efficacy should not be applied in human heart diseases. Ongoing investments into ineffective cell therapies divert funds from methods that merit investigation [185]. Some patients pay for the treatment; but valuable experience is partly lost because conflicted researchers tend to overestimate positive results leaving adverse effects out of attention. One of the objections to prohibitive measures [199, 200] is that the hope is taken from severely ill patients. Obviously, therapeutic methods with unproven effects should be tested in high-quality research shielded from bias. Patients participating in such research must be treated free of charge. As for animal experiments, they should also be performed by researchers not influenced by conflicts of interest.

CONCLUSION

The deception is objectionable on the grounds that it limits autonomy and breaches trust; these grounds possibly do not apply to placebos when they are prescribed under appropriate ethical and clinical conditions, although it can be problematic both on the professional and ethical level [201, 202]. In other words, placebo therapy with misinformation of a patient can be justifiable and beneficial [203]; but it is still not a sufficient reason to publish biased information.

As mentioned in the introduction, the quality of scientific argumentation seems to have deteriorated in some parts of the world during the last decades. It has become a usual practice to disregard published criticism in spite of personal communications and debates at conferences. Apparently, certain scientists make use of critical comments without citing them, or just continue publications disregarding the criticism [61, 204]. The same scientists continue working sometimes in cooperation with renowned researchers, while it is possible that some later reports are more reliable than earlier ones. However, it is not enough to hope that reliable papers would be sooner or later confirmed while forgeries will fall into oblivion. Biased papers are misleading for research and practice, cause losses of time and money. Wrong concepts are persisting and reappearing, which may result in useless experimentation and application of invasive methods without indications [197, 204, 205]. Some scientific writers have perfected themselves in tangling their texts, making evaluation increasingly difficult. Considering the "improvement" of fraudulent skills, researchers, editors, and authorities must take coordinated measures to support integrity in medical research and practice [206]. An important factor contributing to scientific misconduct is a hidden conflict of interest [196]. Marketing of placebos in the guise of evidence-based medications seems to be on the increase. The response to misconduct needs national and international bodies to provide leadership and guidelines [206]. In Russia, there is the Higher Attestation Commission, commonly known as VAK, the main purpose of which is the maintenance of the high quality of scientific research. The VAK awards or approves of all academic degrees. However, many such degrees have been awarded on the basis of works with detectable trimming of data, manipulations with statistics, misquoting and plagiarism [196, 207].

The matters discussed here are only a tip of the iceberg. Related topics reported previously and not included in this and preceding [1] reviews are doubtful effects of calf hemodialysate and policosanol, invasive procedures and organ biopsies with questionable indications *etc.* [197, 204, 205, 208, 209]. Some of the questions are not entirely clear, so that further research and reviews of the literature are needed.

CURRENT & FUTURE DEVELOPMENTS

Some topics discussed in this review might be not completely clarified so that arguments provided here might induce a constructive discussion. Certainly, not only discussions but also further studies are needed, evaluating treatments methods, drugs and dietary supplements with un-

proven effects. Practical recommendations must be based on the research of high quality not influenced by conflicts of interest. Only such studies should be included in reviews and meta-analyses. The problem is how to distinguish between reliable and unreliable works and how to ensure the high quality and independence of medical research. In view of the proliferation of papers having questionable reliability and growing disregard for laws and regulations at least in some parts of the world, we see only one solution, already mentioned in the Conclusion: researchers, editors, and authorities should take coordinated measures to support integrity in medical research and practice. Governmental agencies may have methods at their disposal that would help to uncover dishonest and/or irresponsible attitude to the medical research and practice. The response to misconduct in medical research and practice needs national and international bodies to provide leadership and guidelines [206]. Editors should publish comments and letters containing sound criticism seeing that the criticized authors don't disregard published comments e.g. [61,197,204,205,208] but comprehensively and objectively discuss all relevant publications. The peer review and publication process should become more transparent, among others, to identify biased reviewers. Furthermore, many patients pay for treatments having unproven efficiency (e.g. some stem cell therapies), but the experience is partly lost for science as conflicted researchers tend to overestimate positive results, if there are any, leaving adverse effects out of attention. Therapeutic methods with unproven effects should be applied within the framework of high-quality research, as far as possible free for patients, who must be comprehensively informed about potential risks and benefits.

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