

Letter to the Editor

Integrating medical knowledge to improve science with a novel, straightforward attitude: the bio-integrative medicine

Dear Editor,

Progressing on the scientific pathway should mean accounting on a pluralistic attitude and on a rigorous approach to deal with any natural event occurring in the human life. Progressing means describing, interpreting and addressing the phenomena with the exclusive tools of rationality, experimental trials and criticism in the widest debate expanded among experts and ultimately to use novelties coming from research in order to ameliorate the human existence. The SARS-CoV2 pandemic burst a dramatic crisis inside the aforementioned tenets. COVID-19 emergency abruptly put people outside their previous trust in science, decidedly throwing many individuals into the darkness of an averted obscurantism and superstitious beliefs¹⁻⁷.

Pluralism in science has to be considered a sort of priceless wealth but probably the dramatic urgency in addressing the COVID-19 pandemic hampered the cautious debate in science to primarily focus onto immediate and sound solutions⁵. Yet, any intervention in the biomedical science needs to integrate different skills in order to prevent hasty decision-makings and clumsy recommendations. For example, regarding COVID-19 pathogenesis and the consequent therapy, turn-around time discourses and wasting time suggestions ruled out a sound debate within the expert community to highlight the nature of pandemic. Pharmacological novelties should include sound research on newly discovered nature-derived substances, yet the rationale underlying the use of herbal therapy is confined to folk and traditional medicine, instead of building up a new kind of speech about integrative medical sciences⁶. Integration is not merely the merging of different, quite irreconcilable tenets, as for instance in this case: if pharmacology is grounded on raw chemistry, homeopathy yet is not, therefore integration is erroneously meant as the civil coexistence of two different cultures, two different perspectives, two different approaches, without any “real” integration to generate a novel kind of medical science, based on the “good things”, which each other could offer. In this circumstance, integration is intended as the effort to income a puzzling, strange or an odd medical practice in the evidence-based medicine (EBM). This might be even hazardous for science, which should experience a sort of spoiling pollution.

Yet, many good ideas in oncology and other chronic inflammatory ailments, in degenerative disorders and metabolic diseases, took advantages by capturing evidence from folk medicine but not necessarily by using the same methodology. Briefly speaking, the discriminant between experimental EBM and traditional or complementary medicine is the “reproducibility of data by a standardized methodology” for the first and “the occurrence of an effect (usually healing) by using the same practice” for the second. Obviously, patient’s healing is a highly complex topic and without a rigorous traceability of the phenomena underneath the observed outcome, it is very hard to dismiss the questionable possibility that healing was not due to the adopted practice. Therefore, this is the land, the scenery, where the integration should be attempted: trying to tailor the best tools to perceive the real nature underlying any observed event.

Clinical literature is quite scant of sound and reliable papers describing the effect of nature-derived substances in cancer. The number of clinical trials using plant derived flavonoids in cancer is approximately 2% (1.93%) of all papers in PubMed/Medline dealing with the research of these polyphenols in cancer. Usually, active molecules are introduced in humans as nutraceuticals, i.e., supplementation with diet, but rarely these RCTs are “purified” from statistic confounders, such as dietary habits, lifestyles, presence of comorbidities, age, gender and sample stratification. Moreover, flavonoids as nutraceuticals elicit some benefits, do not modify the existing pathology, so acting as ancillary “pro-drugs” to reduce and alleviate possible exacerbations due to the tumor.

However, the role of plant flavonoids has become particularly important for having introduced the “hormetic” principle in science.

Pharmaceuticals are believed to act linearly, i.e., in a linear dose-dependent modality. Recent data reported that oxygen reactive species (ROS) mainly act as signaling molecules⁸. Therefore, their elicitation by subtle biomolecular events, such as those modulating the complex relationship between mitochondria and other intracellular compartments and organelles, triggers cell survival programs, oxidative stress response, the homeostatic balance between Nrf2 (antioxidant pathway) and NF-κB (pro-inflammatory pathway), autophagy and apoptosis promotion in cancer cells, regulation of the cell cycle, cell differentiation. Paradoxically, ROS are fundamental actors of the complex machinery of cell survival and those substances able to tune this machinery are paradoxically toxic compounds such as plant polyphenols, chemical xenobiotics, physical insults and ozone. Interestingly, medicine seems to turn back to snakes and venoms, in a symbolic way. The experimental use of plant-derived toxicants, such as flavonoids, allowed researchers to unveil the intriguing and puzzling mechanism of mitohormesis⁹, which stands to date as the only principle able to explain the beneficial effect of oxidized aldehydes and lipidic peroxides generated by ozone in medicine, even in COVID-19 therapy¹⁰.

Therefore, what is the real challenge we should face?

Medicine is particularly hungry of novelties, functional antibiotics are reducing in number due to multidrug resistant strains in hospital environments, tailoring molecules by *in silico* studies is a very expensive, cumbersome and time-consuming enterprise, people need a medical safety and assistance much keener and more functional than before.

The novel bio-integrative medicine should be nourished by intriguing issues in the cell and molecular bioscience, in chemical and physical science, which may from the open-minded experimental investigation even on substances from folk and traditional medicine. Knowledge is a wealth with no single master but endowed of many appliers, each able to be a great master for himself, before being a new knowledge for anyone.

Conflict of interest

The authors state they have no conflict of interest.

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