British Journal of Nutrition (2022), 127, 1034–1036 doi:10.1017/S0007114521004852

Reflections on 'The biological action of saponins in animal systems: a review'

George Francis, Zohar Kerem, Harinder P. S. Makkar and Klaus Becker

The biological action of saponins in animal systems: a review

George Francis[1], Zohar Kerem[2], Harinder P. S. Makkar[3] and Klaus Becker[1]*

[1]*Department of Aquaculture Systems and Animal Nutrition, Institute for Animal Production in the Tropics and Subtropics, University of Hohenheim (480), D 70593 Stuttgart, Germany*

[2]*Institute of Biochemistry, Food Science and Nutrition, Faculty of Agricultural, Food and Environmental Quality Sciences, The Hebrew University of Jerusalem, P.O.B. 12, Rehovot 76100, Israel*

[3]*Animal Production and Health Section, International Atomic Energy Agency, P.O. Box 100, Wagramerstr. 5, A-1400 Vienna, Austria*

(Received 4 December 2001 – Revised 19 June 2002 – Accepted 11 August 2002)

Saponins are steroid or triterpenoid glycosides, common in a large number of plants and plant products that are important in human and animal nutrition. Several biological effects have been ascribed to saponins. Extensive research has been carried out into the membrane-permeabilising, immunostimulant, hypocholesterolaemic and anticarcinogenic properties of saponins and they have also been found to significantly affect growth, feed intake and reproduction in animals. These structurally diverse compounds have also been observed to kill protozoans and molluscs, to be antioxidants, to impair the digestion of protein and the uptake of vitamins and minerals in the gut, to cause hypoglycaemia, and to act as antifungal and antiviral agents. These compounds can thus affect animals in a host of different ways both positive and negative.

Saponins: Steroids: Triterpenoids: Biological activity

Fig. 1. Screenshot of the abstract of the review article.

It is encouraging and honouring to note the high resonance that our review article on saponins found among the research community.

Saponins, secondary metabolites, constitute a large family of diverse natural glycosides produced almost solely by plants[(1)]. They possess many medicinal properties and unique surfactant activities that are sought for and used by the food and cosmetic industries. In our experiments, they improved growth and decreased metabolic rate (mg oxygen consumed/kg metabolic body weight/h) in different fish species (common carp and Nile tilapia) when present in the diet. The latter effects were achieved by adding, for example, as little as 150 mg/kg of a Quillaja saponin concentrate to the fish diets. In common carp, such a low dietary supplementation acted as a growth stimulant over an 8-week feeding period[(2)]. The consumption of saponins also decreased the metabolic rate, even while increasing growth and feed conversion efficiency. In Nile tilapia, similar effects were observed at a higher dietary supplementation rate of 300 mg/kg (S300 group) over a 14-week feeding period[(3)]. While saponins have been well known to the scientific and to the industrial worlds as compounds occurring in traditional medicines, little was known then about their mechanisms of action, for example, concerning protein utilisation, growth stimulation, fish reproduction, metabolic rates, among others.

In fish as well as ruminants, we found that adding saponins to diets apparently leads to a more efficient protein utilisation and a higher feed energy retention. In addition, saponin supplementation also inhibited egg-laying behaviour of female Nile tilapia, an important property with potential uses in commercial aquaculture. The higher supplementation (S300) prevented eggs production during an entire 14-week period in Nile tilapia, compared with regular egg production and mouth brooding in the female fish of the control group. Cholesterol lowering in animals and humans was also proposed by many, without explaining how a compound too large to be absorbed from the intestine actually operates in the body. In fish, muscle cholesterol level was significantly higher than that of the control group[(3)]. These unexpected effects, important for both science and agri-food production applications, in view of for example the recognised lethal effects of saponins in water on fish in ponds, provided the impetus to highlight possible mechanisms of action when saponins are used as a dietary supplementation. The 2002 review aimed to collate the scattered information published under different names and ontologies, to provide insights into

the biological effects of saponins, to initiate the unification of an ontology and to stimulate further research interest in these interesting diverse compounds.

Contents and relevance

The paper dealt with the complex multidimensional matrix, bringing together chemistry, biochemistry and pharmacology of saponins in aquaculture and other animal systems, and their impact on human and animal nutrition, and pharmacology. The paper presented the vast and sometimes divergent knowledge of saponins. On the one hand, these compounds are a rather related family of natural glycosides, all synthesised from monoterpenes and monosaccharides and, on the other hand, they possess an array of biological activities. The high occurrence of saponins in medicinal and edible plants, and the overwhelming diverse biological effects of saponin concentrates, purified saponins and even foods containing saponin-rich plant as ingredients were reviewed. These effects sometimes appear to be contradictory in nature, depending on the design and the model, and they include:

- Transient membrane-permeabilising activity possessed by a large number of saponins, irrespective of whether having a triterpenoid or a steroid aglycon.
- Adjuvant effects of selected saponins and their derivatives that can promote specific immune system function, leading to these compounds serving as pharmaceuticals.
- Cytostatic and lethal effects on various cancer cells, in culture and in animal models.
- Cholesterol lowering effects in animals and humans.
- Antidiabetic actions that may not always relate to cholesterol lowering.
- Growth promoting effects of saponin in animals when used as dietary supplements.
- Metabolic rate lowering effect.
- Anti-feedant and insecticidal actions.
- Molluscicidal, antiviral, antiprotozoal and antimicrobial activities.
- Surfactant activities and micelle formation that give them several food and non-food applications including, lately their use even in the production of novel biodegradable inks.

While interpreting the biological effects of saponins in biological systems, the difficulty in establishing structure–activity relationships surfaced. During preparation of the review, the study of the scientific literature revealed lack of established and accepted links of the vast diversity of naturally occurring saponins (indeed closely related to their chemical structures) with specific effects that are achieved only by a few. It was and is still apparent that most published work is limited to detailing the observed activities and fall short in providing mechanisms of actions.

In view of their widespread presence in animal and in human diets, we tried to highlight topics that may be important for further investigation, for example, the potential effects of saponins or their derivatives on animal and human reproductive cycles and hormonal balance; the interactions of dietary saponins with other dietary constituents; their actions in the gut and their possible effects on the gut microbiome, among others.

The article became popular among researchers, as we can analyse today, mainly due to: (1) the well-designed collation, taking into account the extent of published data, scope and audience; (2) the attempted interpretation of relevant research data that made it easier for peers to identify interesting research questions related to saponins and (3) the increased interest of the research community in biologically active plant secondary metabolites, in which case the review helped in identifying activity pathways and the interpretation of research results.

In recent decades, accumulating studies using hyphenated modern analytical tools serve to better decipher the structures of known and recently identified saponins and their metabolites in the body[4]. Large datasets of genomes of plants, animals and human, and transcriptomes, as well as the statistical tools to investigate them became available. We harness these to continue with the unification of ontologies and to achieve the formulation of structure–activity relationships. Today we use computer-assisted prediction tools, such as docking and molecular dynamics to explore the action of saponins[5] including antiviral effects against a novel strain of coronavirus named SARS-CoV-2[6] and their effects on enzymes such as the Cytochromes P450 CYP3A4 and CYP19A1 (AKA aromatase or oestrogen synthase), and their upstream receptors pregnane X receptor and the aryl hydrocarbon receptor that are responsible, for example, to metabolise both drugs and steroidal hormones[7,8]. These may contribute to our better understanding of how specific saponins indeed affect both growth, protein utilisation and egg-laying in fish.

Follow-up work

The review also helped us in explaining the results obtained on supplementation of saponins in fish diet. Adaptation to saponins by the biological systems, reported by many researchers and discussed in the review, assisted in planning our future experiments on intermittent supplementation of saponins in fish diets. This approach did not enhance the production observed on continuous supplementation, nevertheless it led to cutting the cost of saponin supplementation without scarifying beneficial responses of the supplementation[9]. These exciting observations extended our research on beneficial effects of saponins on ruminant animal production[10] with a focus on gut microbial ecology and enteric methane reduction[11].

Addition of saponins in a pond has been used to immobilise and capture fish since centuries. A long-established thinking was that saponins are toxic to fish and addition of saponins in diets might lead to fish mortality; however, our research and the review helped in dispensing with this long-held view. Thereafter, several workers started exploring the effects of saponin on fish biology including growth and reproduction, opening a new area of work. Furthermore, our work contributed to change in outlook, from adverse effects of saponins to beneficial ones – from antinutritional factors to bioactive compounds possessing an array of biological activities, in animal production. Other areas that received momentum, thereafter, were better

characterisation and classification of this heterogeneous class of phytochemicals, identification of new sources of saponins, saponin structure–activity relationship, metabolic and functional diversity of saponins, beneficial effects of saponins in human and animal health and production, among others.

References

1. Osbourn AE (2003) Saponins in cereals. *Phytochemistry* **62**, 1–4.
2. Francis G, Makkar HPS & Becker K (2002a) Dietary supplementation with a Quillaja saponin mixture improves growth performance and metabolic efficiency in common carp (*Cyprinus carpio* L). *Aquaculture* **203**, 311–320.
3. Francis G, Makkar HPS & Becker K (2001) Effects of Quillaja saponins on growth, metabolism, egg production, and muscle cholesterol in individually reared Nile tilapia (*Oreochromis niloticus*). *Comp Biochem Physiol* **129**, 105–114.
4. Barbera GL, Capriotti AL, Cavaliere C, *et al.* (2017) Liquid chromatography-high resolution mass spectrometry for the analysis of phytochemicals in vegetal-derived food and beverages. *Food Res Int* **100**, 28–52.
5. Karpagam V, Sathishkumar N, Sathiyamoorthy S, *et al.* (2013) Identification of BACE1 inhibitors from Panax ginseng saponins – an Insilco approach. *Comput Biol Med* **43**, 1037–1044.
6. Falade VA, Adelusi TI, Adedotun IO, *et al.* (2021) In silico investigation of saponins and tannins as potential inhibitors of SARS-CoV-2 main protease (M^{pro}). *In Silico Pharmacol* **9**, 9.
7. Da-Cheng H & Pei-Gen X (2019) Impact of drug metabolism/pharmacokinetics and their relevance upon traditional medicine-based cardiovascular drug research. *Curr Drug Metab* **20**, 556–574.
8. Fatoki TH (2021) Bioinformatics Exploration of Ginseng: A Review. Interchopen Open Book Series 2021. https://www.intechopen.com/online-first/75231 (accessed November 2021).
9. Francis G, Makkar HPS & Becker K (2002b) Effects of cyclic and regular feeding of Quillaja saponin supplemented diet on growth and metabolism of common carp (*Cyprinus carpio* L). *Fish Physiol Biochem* **24**, 343–350.
10. Wina E, Muetzel S & Becker K (2005) The impact of saponins or saponin-containing plant materials on ruminant production: a review. *J Agric Food Chem* **53**, 8093–8105.
11. Goel G, Makkar HPS & Becker K (2008) Changes in microbial population, methanogenesis and rumen fermentation in response to saponin rich fractions of different plant materials. *J Appl Microbiol* **105**, 770–777.

British Journal of Nutrition