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Chapter

Natural Products for Salmonellosis: Last Decade Research

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Abstract

Salmonellosis is a disease of great relevance in terms of public health given the economic and social impact that causes both in developing and highly industrialized countries. Due to its transmission mechanism, it affects hundreds or thousands of people every year and is considered an acute disease of worldwide distribution. Causative agent of salmonellosis is *salmonella* specie which are small gram-negative bacilli and facultative intracellular pathogen of the Enterobacteriaceae family. Multidrug resistance is reported more frequently in strains of *salmonella*, raising the necessity of new strategies to combat its spread and to treat the disease. Natural products (NPs) derived from traditional medicine knowledge have become an important resource to this end. In this chapter, we present a summary of information published from 2010 to 2020, as a sample of the potentiality of NPs as agents for Salmonellosis. This search was not exhaustive, rather, we aim to obtain a random sample of information using the simplest terms on the matter of natural products for salmonellosis, hopefully, as a reference source for interested researchers.

Keywords: *salmonella*, antibacterial activity, natural products, anti-salmonella, Salmonellosis

1. Introduction

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Salmonellosis is a disease of great relevance in terms of public health given the economic and social impact that causes both in developing and highly industrialized countries. Due to its transmission mechanism, it affects hundreds or thousands of people every year and is considered an acute disease of worldwide distribution [1] with variations in the frequency of serotypes from one country to another [2], being notably more frequent in areas that have not reached adequate sanitation and hygiene conditions or that do not have enough resources and public health infrastructure. There is no distinction in the occurrence of salmonellosis by sex, age, or social and economic status with high incidence at the extremes of life, being the most vulnerable groups, children under 5yo, adults over 60 years of age and immunocompromised individuals [3, 4]. On the other hand, it is also a seasonal disease, so incidence is higher on periods of increased environmental temperature like spring and summer, showing a decrease in autumn and winter [5].

The raise in salmonellosis at any part of the world is of maximum relevance. For example, an incidence of 0.78–3.8 million cases per year has been estimated in the United States. Natural reservoir is made up of domestic animals (dogs and cats), wild animals (reptiles such as iguanas and turtles) as well as humans (carriers, convalescent). Transmission is through food (with or without manufacture) and water contaminated with human or animal feces and from individual to individual. Salmonellosis presents as sporadic cases or as outbreaks with variable affectations. Incidence rate is dose-dependent in function of the disseminated serotype and is determined by incubation period, symptoms and severity.

Causative agent of salmonellosis are *salmonella* species, numerous disease outbreaks are related to the consumption of eggs, chicken meat and other raw products (mainly dairy). For instance, in an outbreak of enteric salmonellosis serotype Typhimurium (n = 99) induced by consumption of roast porcine meat in an institution for the mentally ill in Konagua it was shown that the incubation period was between 10–12 hours and that the supply of antibiotics prolonged excreta periods. Salmonellosis due to *Salmonella enterica* serotype Enteritidis was detected in an interstate outbreak in the United States in the early 90's, produced by the consumption of ice cream (224,000 cases) and in Canada due to the consumption of commercial packaged cheese (800 cases). Salmonella Javiana (n = 66) has been reported to produce outbreaks as in Boston due to the consumption of chicken sandwiches [6].

2. Salmonella

Salmonella belongs to the Enterobacteriaceae family, which are small gramnegative bacilli varying in sizes ranging in average from 2–3 μ m in length and 0.4–0.6 μ m in width. These bacilli do not form spores and possess peritrichous flagella hence are mobile microorganisms, although some genera, such as Klebsiella and Shigella, are lacking on these organelles and so on mobility. Traditional grouping classification is carried out using primary biochemical characteristics that allows a further sorting into subgroups based on antigenic structure determinants or using bacteriophage reactions. Currently, with the advances in molecular biology, the differentiation of groups and subgroups can be made using PCR technique for identification, diagnostic and epidemiological purposes.

Regarding its metabolic characteristics, *salmonella* grows in simple synthetic media and can use unique carbon sources, such as glucose in a fermentative way with the subsequent formation of acids and/or gases, reducing nitrates and nitrites, rendering oxidase negative reaction. *Salmonella* also tests positive for methyl red, hydrogen sulfide, indole-ornithine motility (MIO medium), lysine decarboxylase, arginine dihydrolase, ornithine decarboxylase, gas from glucose, and fermentation of numerous carbohydrates such as rhamnose, arabinose, mannitol, etc.

Most enteric microorganisms are resistant to inhibition by the action of certain bacteriostatic dyes, the selective media containing these compounds facilitate considerably isolation from fecal samples, *salmonella* is less sensitive than coliform microorganisms against citrate inhibition action; for instance, SS (Salmonella-Shigella) agar containing both citrate and bile salts is therefore used as a selective medium for the culture of pathogenic species [7, 8].

3. Classification

Although controversial and evolving, there is a *salmonella* nomenclature used by the Centers for Disease Control and Prevention (CDC) and recommended by the

Collaborating Center of the World Health Organization (WHO), which according to the differences in their 16S rRNA sequence analysis classifies this genus into two species, *Salmonella enterica* and *Salmonella bongori*. *S. enterica* can also be further classified into six subspecies mainly found in mammals and is responsible for 99% of infections in humans and warm-blooded animals. On the other hand, *S. bongori* is predominantly environmental and on cold-blooded animals [9].

3.1 Classification according to Kauffmann-White

Since decades ago, classification of salmonella finalizing at the species level are based on its antigenic structure. Although certain strains that have the same antigenic activity could present different metabolic reactions (biotype variants or serotypes), this sorting method is generally accepted and is actively in use.

Surface antigen studies are based on H, O, K and Vi antigens. H is denominated surface or flagellar antigen and participates in host immune response, O (aka somatic antigen) is a lipopolysaccharide located in the cell membrane, K is a capsular antigen and Vi antigen is a subtype of K antigen associated to virulence [9] and the obtention of antisera containing antibodies against all these fractions allows the identification of *salmonella* species. More than 2,500 serotypes have been identified related to the H, O, K and Vi antigens [10] as a result of the numerous absorption tests and cross-reactions studies carried out in Denmark and England by Kauffman and White. Currently, large centers in Copenhagen, London, and Atlanta have the necessary collections of specific antisera for salmonellas typing. In most testing and diagnostic laboratories, *salmonella* strains are identified and classified by their fermentative characteristics and agglutination reactions using group-specific antisera.

In Mexico, for example, a study for the classification and identification of *salmonella* serotypes at public and private health centers and hospitals analyzed 24,394 *salmonella* strains isolated from different sources, 15,843 (64.9%) of human origin and 8,551 (35.1%) non-human demonstrating the usefulness of Kauffmann-White scheme and using antisera produced at the National Institute of Diagnosis and Reference (INDRE) in accordance with the Center for Disease Control and Prevention, Atlanta (GA), showing that most frequent serotypes both in human and non-human samples were *S.* Typhimurium, *S.* Enteritidis, *S.* Derby, *S.* Agona and *S.* Anatum. From the epidemiological point of view, it is interesting to identify which are the circulating and emerging serotypes to implement prevention strategies [8].

4. Pathogenicity

Salmonella spp. is a highly pathogenic microorganism that presents different pathogenicity mechanisms including adherence, invasiveness, colonization and growth, toxicity and tissue damage [11]. It is a facultative intracellular pathogen causing moderate to severe infections, or even compromising systemic infections risking patients' lives, depending on the serotype, virulence, inoculum and immunological state of involved host, and all of this using only a mixture of toxins and other virulence factors.

Clinical manifestations in humans include enteric fevers, acute gastroenteritis and septicemia in extreme cases. Prototypical enteric fevers are caused by *Salmonella* Typhi, this is also known as typhoid fever, after its incubation period (7–14 days), symptoms such as anorexia, headache, followed by general malaise and fever may occur. The interaction patient-causative agent is essential for the progression of the disease, *salmonella* must find a microhabitat suitable for its establishment, multiplication and virulence factors expression.

Salmonella produces at least three toxins: enterotoxin, lipopolysaccharide endotoxin (LPS), and cytotoxin. Enterotoxigenicity, which is a property present in many serotypes of this microorganism, including S. Typhi, is expressed a few hours after contact with the host cell. The pathogenicity mechanisms by which salmonella induces diarrhea and septicemia have not yet been clearly elucidated, but it appears to be a complex phenomenon involving numerous virulence factors such as those mentioned above.

The specific virulence factors are encoded by a group of genes for the formation of pathogenicity islands (SPI), with G + C percentages differing from the average of the bacterial genome. Direct repeats are present at the filament ends, carrying genes that encode mobility factors such as integrases, transposases or insertion sequences and are frequently inserted on tRNA. This suggests that they have been obtained from other species by horizontal transfer or by plasmids. There are numerous genes that participate in the invasion and that are present in salmonellas, genes that code for the synthesis of proteins related to the translocation of effector molecules within the cytoplasm of the host cell. Today, it is known that *salmonella* has five islands of pathogenicity: SPI-1, SPI-2, SPI-3, SPI-4 and SPI-5 [10].

5. Mechanisms of resistance

Drug resistance and worldwide incidence of salmonella infections has been increasingly reported. For example, it has been observed a high incidence among humans, livestock and poultry of *Salmonella enterica* serotype [4, [5],12:i:-], with variants ranging from sensitive- to multi-drug resistant, since the 1990s. Other examples include a strain of *Salmonella enterica* discovered on 2015 that was provided with the gene mcr-1 of plasmid-mediated colistin resistance and clinical isolates from Portugal, China and United Kingdom observed in 2016 with this same gene [12].

Several types of *salmonella* with multi-drug resistance (MDR) are capable of generating diverse types of plasmids, with gene cassettes that provide the property of resistance against antibiotics such as chloramphenicol, tetracycline, ampicillin, and streptomycin [13, 14]. The chromosomal mutation in the regions that determine the resistance to quinolones of the gyrA gene are responsible for the appearance of *salmonella* serotypes with little susceptibility to ciprofloxacin [15]. On the other hand, the mutated genes that code for extended spectrum β -lactamases, are responsible for the serotypes that have begun to develop resistance to cephalosporins [16].

Resistance not only by salmonella, but by other microorganisms are currently a public health problem worldwide, which threatens the prevention, control and treatment of innumerable infectious diseases, having as expected consequences in terms of health and economic impact. This problem was recognized by the World Health Organization and in 2001 this organization published the Global Strategy for the Containment of Antimicrobial Resistance, publicizing interventionist actions to delay the appearance and to reduce the spread of resistant microorganisms [17]. For 2012, WHO proposed a series of actions such as strengthening health services and epidemiological surveillance, regulated use of antimicrobials in hospitals and in communities, promoting the development of new drugs and appropriate vaccines, among others [18]. This problem is one of the reasons for the development of new alternatives, being natural products derived from traditional medicine, one of the most used resources.

6. Traditional medicine and natural products

The origin of Natural and Traditional Medicine is indisputably linked both to human history and to its fight for survival [19]. Written evidence on plants being

used as remedies for disease is as ancient as Mesopotamian tablets, and from there, a nearly endless number of registers in all cultures, supports its essential role on human well-being. Currently, traditional medicine has been delineated as the use of products of natural origin for health preservation, having the so-called Natural Products (NPs) at its focus.

NPs are broadly defined as small molecules produced by a living organism. This definition comprises a wide variety of compounds including the synthesized during basic metabolism (primary metabolites) or as by-products of it (secondary metabolites). Lipids, carbohydrates, proteins and nucleic acids are part of the first kind of NPs, while smaller molecules such as alkaloids, tannins, saponins and flavonoids are examples of secondary metabolites. Many of the latter does not seem to have a metabolic or evolutionary function for the parental organism, but regardless to that, its utility as drugs, preservatives, dyes, food additives and/or antibiotics is undeniable. Its application to counteract the pathogenic microorganisms affecting our specie, alongside side-effects and resistance to antibacterial drugs, is undoubtedly enough motivation for the current formalization and systematization of traditional knowledge, with methodological studies being carried out very frequently nowadays.

There has been an important upturn in the study of compounds of natural origin during the last decade, supported on ethnopharmacological information, folkloric reputation, traditional uses and the existence of previous evidence, and also based on NPs chemical composition and its chemotaxonomic classification. This explosion of information has been enriched primarily through the obtention and separation of crude extracts, essential oils, and/or other types of preparations that are subsequently analyzed for possible biological activities of metabolites or secondary products. Modern experimental strategies have included bioassays (mainly in vitro), development of NP libraries, production of active compounds in cell or tissue cultures, genetic manipulation of organisms, natural combinatorial chemistry, etc. [20]. NPs, being originated in living organisms, are essentially complex mixtures contained within cellular structures, hence the first step into the study of its properties is the separation of such structures. This first step is called extraction, and is generally carried out by liquid solvents at room temperature and atmospheric pressure, along with other well-known and widely used techniques such as steam distillation and the use of supercritical fluids or pressurized gases [21]. The proper choice of an extraction step is necessarily based on the nature, origin and composition of the product to be studied, taking into account the characteristics of the possible solvents (innokenty, reactivity, etc.), toxicity of secondary products, product sufficiency needs and evaluation methods to be followed afterwards, as a whole this step should result suitable to fulfill the objective of a research. Second and third steps are the setting of an adequate model for biological efficacy assessment and the elucidation of individual bioactive components.

In this chapter, we enlisted natural products frequently reported against salmonella from bacteria (**Table 1**), fungus (**Table 2**), animal (**Table 3**), plant (**Table 4**) or combined (**Table 5**) origin, organized on a chronologically descending order according to publishing date. To get a glimpse on the universe of information that NPs research has become, we made a fast search on two commonly used and easily accessible databases (PubMed and Google scholar) for the terms: salmonella, antisalmonella, salmonellosis, natural product and antibacterial activity, alone or in combinations. Search results without the terms salmonella or salmonellosis were excluded. From the remaining registers, we selected those corresponding to experimental reports where the extraction step was performed and thoroughly described by authors. Studies on isolated or synthetic NPs were not included and research on infection or tissue damage protection after salmonella colonization were also excluded. Review articles or abstracts were not considered, although we accounted

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Lactobacillus plantarum ZJ316	Bacteria	culture supernatant filtration (methanol/ acetonitrile)	bacilli	L-phenyl lactic acid	China	Salmonella Paratyphi-A (CMCC 50093), Salmonella Paratyphi-B (CMCC 50094), Salmonella enterica subsp. enterica (ATCC 14028), Salmonella enterica subsp. arizonae (CMCC(B) 47001), Salmonella choleraesuis (ATCC 13312), and Salmonella Typhimurium (CMCC 50015)	2020	[22]
Lectin (Bifidobacterium adolescentis) from bee honey	Bacteria	crude and purified extracts	honey	lectin	Iraq	Salmonella Typhi (clinical isolates)	2019	[23]
Lactobacillus salivarius, L. casei B1, <i>L. plantarum</i> , L. delbrueckii and L. delbrueckii	Bacteria	co-culture	co- culture	not specified	Benin	Salmonella spp., Salmonella Typhimurium (ATCC 14028)	2019	[24]
Lactococcus lactis subsp.lactis (CNRZ 1427)	Bacteria	not specified	not specified	specific microbial enzymes, perox- ide, weak organic acids anti-bacterial peptides, secretion of bacteriocins protease production	Algeria	Salmonella spp. (veterinary isolate). Mice tests	2014	[25]
Streptomyces spp	Bacteria	crude protein	microbial cells	not specified	India	Salmonella Enteritidis	2014	[26]

Table 1.Summary of frequently reported natural products from bacteria origin against salmonella.

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Lentinus edodes	Fungus	fermenting/Black rice bran culture	mycelia	bioprocessed polysaccharide	Korea	Salmonella Typhimurium (SL1344)	2018	[27]
Coriolus versicolor	Fungus	methanolic extract	not specified (probably full fungi body)	phenolics, polysaccharides, β-glucans, α-glucans, proteins	Serbia	Salmonella Enteritidis (ATCC 13076)	2016	[28]
Pleorotus ostreatus (oyster mushroom)	Fungus	ethanolic extract	not specified (probably full fungi body)	not specified	Germany	Salmonella Typhi	2015	[29]
Ganoderma lucidum	Fungus	ethanolic, methanolic, acetone and aqueous extracts	fruiting bodies	not specified	India	Salmonella Typhi (MTCC- 531)	2010	[30]
Lentinus tuberregium	Fungus	Hexane, Dichloromethane, Chloroform and Ethylacetate extracts	not specified (probably full fungi body)	not specified	India	Salmonella Flerineri (M- 1457) Salmonella Typhi (M- 733)	2010	[31]
Pichia pastoris X-33	Yeast	YPD broth supplemented with 1 mg.mL $-$ 1 pancreatin, 0.2% bile salts, and pH adjusted 8 with 0.1 N NaOH	yeast cell	not specified	Brazil	Salmonella Typhimurium (strain 29630)	2015	[32]

Table 2. Summary of frequently reported natural products from fungi origin against salmonella.

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Apitoxin	Animal	crude apitoxin	apitoxin	Melittin, adolapin, apamin or MCD-peptide, phospholipase A2 or hyaluronidase, histamine, epinephrine	Ecuador	Salmonella Anatum, Salmonella enterica subsp. arizonae, Salmonella Bardo, Salmonella Bredeney, Salmonella Dabou, Salmonella Drac, Salmonella Enteritidis, Salmonella Infantis, Salmonella Isangi, Salmonella Montevideo, Salmonella Mbandaka, Salmonella Ndolo, Salmonella Newport, Salmonella Rissen, S. enterica subespecie salamae, Salmonella Seftenberg, S. Stanleyville, S. Thompson and Salmonella Typhimurium	2020	[33]
Apitoxin	Animal	crude apitoxin	apitoxin	Melittin, adolapin, apamin or MCD-peptide, phospholipase A2 or hyaluronidase, histamine, epinephrine	Ecuador	Salmonella Newport, Salmonella Isangi, Salmonella enterica subsp. salame, Salmonella Bardo, Salmonella Infantis, Salmonella Montevideo, Salmonella Stanleyville, Salmonella Ndolo, Salmonella Dabou, Salmonella Typhimurium, Salmonella Enteritidis	2019	[34
Masske butter	Animal	lactic isolates	microbial cells	lactic acid	Iran	Salmonella enterica	2019	[35
Propolis	Animal	ethanolic extract	propolis	flavonoids, alkaloids, terpenoids, steroids, saponins, and tannins	Indonesia	Salmonella spp.	2019	[36
Sarconesiopsis magellanica	Animal	RP-HPLC	larvae	Sarconesin	Colombia	Salmonella enterica (ATCC 13314)	2018	[37
Dadih dadih	Animal	ice cream	buffalo milk yogurt	not specified	Indonesia	Salmonella Typhimurium	2017	[3
Donkey's milk	Animal	no extraction	milk	not specified	Serbia	Salmonella Enteritidis (ATCC 13076) and Salmonella Typhimurium (ATCC 14028)	2017	[39
Colla corii asini	Animal	aqueous and ethanolic extracts	donkey- hide gelatin	glycine, alanine, aspartic acid, glutamic acid, β- amino isobutyric acid	Korea	Salmonella Typhimurium (KCTC 1926)	2017	[40
Bovine natural antibodies	Animal	antibodies	serum	antibodies	The Netherlands	Salmonella Typhimurium (SL3261)	2016	[4
Propolis	Animal	ethanolic extracts	propolis	phenolic acid components. Sinergy with cefixime	India	Salmonella Typhimurium (MTCC 98)	2016	[4
Anguilla spp.	Animal	aqueous dilution	mucus	not specified	Indonesia	Salmonella Typhi	2016	[4:

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Propolis	Animal	not specified	propolis	phenolic compounds (flavonoids)	Chile	Salmonella Enteritidis	2015	[44]
Honeys	Animal	aqueous dilution	honey	not specified	Pakistan	Salmonella Typhi	2015	[45]
Platelet rich plasma	Animal	whole blood	thrombin PRP/CaCl2 PRP	probably antimicrobial peptides	Iran	Salmonella enterica	2014	[46]
Honey	Animal	aqueous dilution	honey	not specified	Romania	Salmonella Enteritidis (ATCC 13076)	2014	[47]
Donkey's milk	Animal	no extraction	milk	not specified	Serbia	Salmonella Enteritidis (ATCC 13076), Salmonella Typhimurium (ATCC 14028), Salmonella Livingstone	2014	[48]
Propolis	Animal	ethanolic, methanolic and aqueous extracts	propolis	terpenoids, flavonoids, alkaloids, phenols, tannins and saponins	India	Salmonella Typhimurium	2013	[49]
Slovenian Propolis	Animal	70% and 96% ethanol	propolis	phenolic compounds (probably a synergy)	Slovenia	Salmonella Typhimurium (14028), Salmonella Enteritidis (ZM138)	2012	[50]
Shrimp Chitosan	Animal	acetic acid 1%	shrimp	not specified	Bangladesh	Salmonella Parathypi	2011	[51]
Honey	animal	saline dilution	honey	not specified	Greece	Salmonella Typhimurium Salmonella enterica subsp. enterica (ATCC 13311) and Salmonella Typhimurium and Salmonella	2011	[52]
Propolis	Animal	ethanolic extract	propolis	quercetin, chrysin, 4′,5-dihydroxy-7- methoxyflavonone and 3,4′,7- trimethoxyflavonone	Turkey	Salmonella Enteritidis (ATCC 13076)	2011	[53]
Honey	Animal	aqueous dilution	honey	not specified	India	Salmonella enterica serovar Typhi	2010	[54]

Table 3.Summary of frequently reported natural products from animal origin against salmonella.

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Zanthoxylum Acanthopodium DC	Plant	n-hexane and ethyl acetate extract	Fruit	flavonoids, alkaloids, and saponins	Indonesia	Salmonella Typhi	2020	[55]
Aleurites moluccana	Plant	methanol extracts	stem bark	scopoletin	Indonesia	Salmonella Typhimurium	2020	[56]
Combre tummicranthum; Acacianilotica and Phyllanthus pentandrus	Plant	aqueous, ethanol and chloroform extracts	leaves	tannins, flavonoids, saponins, sterols, triterpenes, alkaloids, anthocyanes and free anthraquinones	Niger	Salmonella Typhimurim, Salmonella Typhi, Salmonella ParaTyphi, Salmonella Typhimurim, and Salmonella Derby	2020	[57]
Nauclea latifolia	Plant	ethyl acetate and methanol	leaves	tannins, flavonoids and anthraquinones (all are highly polar and polyphenolic) as secondary metabolites but steroids were absent	Indonesia	Salmonella Typhi (clinical isolates, MDR)	2020	[58]
Hippobroma longiflora	Plant	ethanolic extracts	leaves	alkaloids, flavonoids and saponins		Salmonella Typhi	2020	[59]
Biarum bovei (cardin)	Plant	ethanol 50% (ultrasound)	leaves	Nerrel, flavonoids and nercernerrel	Iran	Salmonella Enteritidis (CMCC 50041)	2020	[60]
Trema orientalis L. Blumae (anggrung)	Plant	methanol extracts	leaves	alkaloid, flavonoids, tannins, terpenoids, steroids, saponin, phenolic	Indonesia	Salmonella spp.	2020	[61]
<i>Agave tequilana</i> Weber var. azul	Plant	flour	leaves	Fructans	Mexico	Salmonella Typhimurium	2020	[62]
Clerodendrum fragrans Vent Willd	Plant	methanol, ethyl acetate and n- hexane (chromatography)	leaves	Tannins and flavonoids	Indonesia	Salmonella enterica (ATCC 14028)	2020	[63]
Canarium schweinfurthii	Plant	hydro-ethanolic extract followed by chloroform and ethyl acetate	stem bark	maniladiol, scopoletin, ethyl gallate and Gallic acid	Cameroon	Salmonella Typhi, Salmonella Enteritidis and Salmonella Typhimurium (clinical isolates) and Salmonella Typhi (ATCC6539)	2020	[64]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Garcinia kola and Alchornea cordifolia	Plant	hydro-ethanolic and methanolic extracts	leaves, root and stem bark	Anthocyanins, Flavonoids, Glycosides, Phenols, Tannins, Triterpenoids and Steroids	Cameroon	S. Typhi (collection), S. Typhimurium and S. Enteritidis (clinical isolates)	2020	[65]
Ziziphus lotus and Ziziphus mauritianas	Plant	methanolic extracts	leaves, fruits and seeds	Quinic acid, p-coumaric acid, rutin and quercitrin	Tunisia	Salmonella Typhimurium (NRLB4420)	2020	[66]
Rhododendron arboreum and <i>Justicia adhatoda</i>	Plant	ethanolic and methanolic extracts	leaves	oleanadien-3β-ethan-3-oate	Nepal	Salmonella enterica subsp. enterica (ATCC 13076)	2020	[67]
Uvaria chamae, <i>Lantana</i> camara and Phyllantus amarus	Plant	aqueous and ethanolic extracts	leaves and root	not specified	Benin	Salmonella Typhimurium ATCC 14028 and Salmonella spp. (isolates)	2020	[68]
Vitis vinifera var. Albariño	Plant	hydro-organic extraction (patented)	fruit	HOL: catechin, epicate-chin and isoquercetin. HOP: phologlucinic acid, miquelianin, rutin, inkaempferol and caftaric acid	Spain	Salmonella enterica subsp. enterica (CECT 554)	2020	[69]
Citrus hystrix	Plant	ethanolic extract	peel	not specified	Indonesia	Salmonella Typhimurium	2020	[70]
Olive oil	Plant	ethanolic extract	fruit	polyphenol extracts	China	Salmonella Typhimurium (ATCC 14028)	2020	[71]
Agrimonia pilosa Ledeb, <i>Iris</i> domestica (L.) Goldblatt and Mabb, Anemone chinensis Bunge,	Plant	aqueous extracts	herb, rhizome, root and tuber	not specified	China	Salmonella Enteritidis (NCTC 0074, 1F6144, LE103 and QA04/19)	2020	[72]
Litsea cubeba	Plant	essential oil	fruit	2,6-octadienal, 3,7-dimethyl-, 2,6-octadien-1-ol, 3,7- dimethyl-, and Z-2,6-octadien- 1-ol, 3,7-dimethyl, Z-2,6- Octadienal, 3,7-dimethyl-, Z- citral	China	Salmonella enterica (CGMCC 1.755)	2020	[73]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Quercus infectoria, Phyllanthus emblica	Plant	aqueous, methanolic and ethanolic extracts	gall, fruit	hexadecanoid acid, 9- octadecenoic acid, octadecenoic acid, 2-tert buil- 4-isopropil-5 metylphenol	India	Salmonella Enteritidis and Salmonella Typhi	2020	[74]
Capparis decidua	Plant	methanolic extract	whole plant	not specified	Pakistan	Salmonella Typhi	2020	[75]
Detarium microcarpum Guill. & Perr.	Plant	ethanolic extract	leaves, twigs, roots, and root bark	flavonoids, sterols, triterpenes, glucosides, coumarins, and saponins	Cameroon	Salmonella Typhi (ATCC 19430), Salmonella Enteritidis (ATCC 13076)	2020	[76]
Tetrapleura tetraptera	Plant	ethanolic extract	stem	citral, acetic acid, limonene, butanol, 2-hydroxyl-3 butanone, Cis-Verbenol Trans- Verbenol, α-Terpinyl acetate, butanoic acid, 2-methyl butanol	Ghana	Salmonella Enteritidis (CICC 21482) and Salmonella Typhimurium (CICC 21483)	2020	[77]
Ocimum gratissimum	Plant	aqueous and ethanolic extracts	leaves	alkaloid, tannins, oxalate, flavonoids and essential oil	Nigeria	Samonella Typhi and Salmonella ParaTyphi (clinical isolates)	2019	[78]
Aeollanthus pubescens	Plant	essential oil (aqueous)	leaves	thymol and carvacrol (anti- radical activity)	Nigeria	Salmonella spp. (multidrug resistant isolate)	2019	[79]
Annona muricata L.	Plant	ethanol extracts	flower	secondary metabolites such as alkaloids, phenolic and flavonoid	Indonesia	Salmonella Enteritidis	2019	[80]
Rhodomyrtus tomentosa (Ait) Hassk	Plant	N-hexane, ethyl acetate, ethanol	leaves	phenols and flavonoids	Indonesia	Salmonella Typhi	2019	[81]
Morinda lucida	Plant	acetone and aqueous extracts	leaves	not specified	South africa	Salmonella enterica subsp. enterica including S. enterica serovar Gallinarum, Dublin, choleraesuis, Braenderup, Idikan, Kottbus, Typhimurium and Enteritidis	2019	[82]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Zanthoxylum acanthopodium DC (andaliman)	Plant	ethanol extracts	fruit	saponin, tannin, steroid and alkaloid	Indonesia	Salmonella Typhi	2019	[83]
Physalis peruviana L	Plant	ethanol extracts	berries and leaves	Phenolic compounds (1- hexanol, eucalyptol and 4- terpenol)	Ecuador	Salmonella spp. (clinical isolates)	2019	[84]
Carica papaya L.	Plant	70% ethanol, followed by n- hexane, ethyl acetate and water	seeds	alkaloids, flavonoids, terpenoids and saponins	Indonesia	Salmonella Typhi (ATCC 1408)	2019	[85]
Psidium guajava	Plant	methanol and aqueous extracts	leaves and stem bark	alkaloid, saponin, phenol, flavonoids, glycoside, anthraquinones, terpenoid and tannin	Nigeria	Salmonella Typhi (clinical isolates)	2019	[86]
Artocarpus heterophyllus. Lamk.	Plant	ethanol extracts	leaves	Saponin, flavonoids, terpenoid/steroids and tannin	Indonesia	Salmonella Typhi	2019	[87]
Sesbiana grandiflora L. Press	Plant	90% ethanol followed by n- hexane, ethyl acetate and aqueous extraction	leaves	Saponin, flavonoids, terpenoid, alkaloids and tannin	Indonesia	Salmonella Typhi	2020	[88]
Myristica fragrans	Plant	aqueous extract	seeds	methane, oxybis [dichloro-, 1H-Cyclopenta [c] furan-3- (3aH)-one,6,6a-dihydro-1- (1,3-dioxolan-2-yl)-,(3aR, 1-t, Octadecane, 6-methyl-, Heptadecane, 2,6,10,14- tetramethyl-, BIS (2- Ethylhextl) phthalate, 4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy- 6-methyl-, 3,4- Dichlorophenethylamine and 1,4-Benzenediol, 2-bromo-	India	MDR Salmonella Typhi isolates (MCASMZU1–13)	2020	[89]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Kalanchoe brasiliensis Cambess.	Plant	hydroethanolic extract	leaves	flavones and flavonols (3- hydroxyflavones or flavonols with substituted 3-hydroxyl groups (methylated or glycosylated))	Brazil	Salmonella Gastroenteritis	2019	[90]
White mustard	Plant	essential oil	essential oil	not specified. Synergic with carvacrol and thymol	USA	Salmonella Typhimurium	2019	[91]
Quercus variabilis Blume	Plant	70% ethanol followed by petroleum ether, ethyl acetate, n-butanol and water	valonia and shell	ellagic acid, theophylline, caffeic acid and tannin acid	China	Salmonella Paratyphi A, Salmonella Typhimurium and Salmonella Enteritidis	2019	[92]
Melia azedarach	Plant	ethanol, ethylacetate, hexane, dichloromethane and methanol extracts	leaves	not specified	Syria	Salmonella Typhi	2019	[93]
Ocotea minarum	Plant	80% ethanol followed by hexane and ethyl acetate	leaves and stem bark	caffeic acid, p-coumaric acid, rosmarinic acid, quercetin and luteolin	Brazil	Salmonella Typhimurium (14028), Salmonella Enteritidis (13076)	2019	[94]
Zingiber zerumbet	Plant	ethanolic extract	rhizome	Alkaloids, terpenoids, and tannins	Indonesia	S. Enteritidis (ATCC 31194) and Salmonella Typhimurium (ATCC 23564)	2019	[95]
Annona muricata	Plant	ethanolic extract	leaves	flavonoids, alkaloids, terpenoids, saponins, coumarins, lactones,	Indonesia	Salmonella Typhimurium (FNCC-0050)	2019	[96]
Ligustrum lucidum Ait, Lysimachia christinae Hance, Mentha piperita Linn and Cinnamomum cassia Presl	Plant	aqueous extracts	fruits, whole plants, leaves, and barks	phenolic acid and flavonoid	China	S. Typhimurium (ST21) (used for prevent contracting infection)	2019	[97]
Pectin of Spondias dulcis	Plant	aqua, ethanol	Fruit peel	oligosaccharides	Cameroon	Salmonella Typhimurium (ATTC 2680), Salmonella Typhimurium (ATTC 2488) and Salmonella choleraesuis	2019	[98]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Acacia farnesiana	Plant	hexanic, chloroform, methanolic and aqueous extracts	fruits	methylgallate, gallicacid and (2S)-naringenin-7-O-β- glucopyranoside	Mexico	Salmonella Enteritidis (ATCC857)	2019	[99]
Adansonia digitata	Plant	aqueous, ethanolic and chloroform extract	leaves and stem bark	alkaloid, flavonoids and tannin	Nigeria	Salmonella Typhi (clinical isolate)	2018	[100]
Cassia occidentalis	Plant	aqueous extract	leaves	saponin, flavonoids, and tannins, glycoside, cardiac glycosides, steroids, saponin glycoside, anthraquinones and volatile oil (trace)	Nigeria	Salmonella Typhimurium	2018	[101]
Benincasa hispida Thunb (Bligo fruit)	Plant	ethanol extracts (96, 70 and 50%)	fruit	not specified (probably a polar molecule)	Indonesia	Salmonella Typhi	2018	[102]
Citrus sinensis (L) Osbeck	Plant	aqueous and ethanol (80%) extracts	peel	alkaloid, tannin, saponin, glycoside, flavonoid, terpenoid, and Phenols	Nigeria	Salmonella Typhi (clinical isolate)	2018	[103]
Cinammomum cassia	Plant	Sodium bisulfite (1:1), petroleum ether	oil	cinnamaldehyde	Indonesia	Salmonella Typhi	2018	[104]
Piper aduncum subsp. ossanum (C. DC.) Saralegui, Piper aduncum L. subsp. aduncum, Mentha piperita L., Mentha spicata L., Ocimum basilicum var. genovese L. Ocimum gratissimum L., Rosmarinus officinalis L., Thymus vulgaris L., Melaleuca quinquenervia (Cav) S.T. Blake, Eugenia axillaris L., Citrus sinensis (L.) Osbeck, Citrus paradisi Macfad, Curcuma longa L., Lippia graveolens (Kunth)	Plant	essential oil (aqueous)	not specified	Probably trans- cinamaldehyde, carvacrol, eugenol and acid 2,4 dihydroxybenzoic	Cuba	Salmonella Typhimurium (ATCC14028), Salmonella enterica subsp. enterica CENLAC (S02, S04, S06, S08, S10), Salmonella enterica (Sc1) isolated from a pig	2018	[105]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Jacaranda micrantha	Plant	aqueos and 70% ethanolextract	leaves	phenolic compounds, tannins, flavones and saponins	Brazil	Salmonella choleraesuis (ATCC 10708) and Salmonella spp. (food isolated)	2018	[106]
Allium sativum and Zataria multiflora Boiss	Plant	aqueous oil extract	bulb and whole plant	Allicin and thymol	Egypt	Salmonella Typhimurium, Salmonella Anatum, Salmonella Lagos and Salmonella Kentucky	2018	[107]
Cinnamomum zeylanicum, Eugenia caryophyllata, Origanum vulgare, Thymus vulgaris and Thymus zygis	Plant	essential oil	bark, bud, flowering plant, leaves and flowers	cinnamaldehyde, linalool, eugenol, eugenyl acetate, b- Caryophyllene, carvacrol, thymol, y-Terpinene, geraniol and p-Cymene.	Spain	Salmonella Typhimurium (ATCC14028), Salmonella Typhimurium and Salmonella Enteritidis	2018	[108]
Citrus medica, Citrus limon and Citrus microcarpa	Plant	juice (pure extract)	fruit	citric acid, hesperidin, carvacrol and thymol	Korea	Salmonella Typhimurium (ATCC 14028, 19585, and DT104 Killercow)	2018	[109]
Equisetum telmateia	Plant	ethanolic extract followed by petroleum ether, dichloromethane (DCM), ethyl acetate (EtAc) and n- Butanol (n-BuOH). Supercritical extract	stem	Kaempferol 3-O-(6"-O- acetylglucoside), 5-O-Caffeoyl shikimic acid, Catechin	Iran	Salmonella Typhi (PTCC 1609)	2018	[110]
Thymus vulgaris L., Rosmarinus officinalis L.	Plant	essential oils	leaves	a-pinene, Thymol, Oxygenated monoterpenes, monoterpene hydrocarbons, borneol, 1,8-cineole	Morocco	Salmonella Typhimurium (ATCC 14028)	2018	[111]
Gracilaria verrucosa	Plant (algae)	aqueous, methanolic and ethanolic extracts	whole plant	carvacrol, p-cymene and y- terpinene	Indonesia	Salmonella Typhimurium	2018	[112]
Sterculia spp.	Plant	ethanolic extract	bark	flavonoids, alkaloids and saponins	Indonesia	Salmonella Typhi	2018	[113]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Nigella sativa	Plant	aqueous and methanolic extracts and oil	seed	not specified	Pakistan	Salmonella enterica	2018	[114]
Rice hull smoke extract	Plant	pyrolysis of rice hulls followed by liquefaction	hull	161 components, bioactive unknown	Korea	Salmonella Typhimurium (CCARM8107)	2018	[115]
Basil, ginger, hyssop, caraway, juniper, and sage	Plant	essential oils	several	estragole, cis-pinocamphone, alpha-pinene (in juniper EO), a-thujone (in sage EO), carvone (in caraway EO) and curcumene (in ginger EO)	Serbia	Salmonella enterica	2017	[116]
Ipomoea aquatica	Plant	ethanolic and methanolic extracts	leaves	flavonoids	Malaysia	Salmonella Typhi	2017	[117]
Andrographis paniculata	Plant	methanolic, ethanolic and acetone extracts	leaves	not specified	India	Salmonella Typhi (clinical isolates)	2017	[118]
Senna occidentalis	Plant	methanolic extract	root and leaves	flavonoid, tannins, saponins, cardial glycoside	Nigeria	Salmonella Typhi	2017	[119]
Grewia flava	Plant	acetone, methanolic, acetylacetate and aqueous extracts	berries, leaves, bark and roots	pelargonidin 3,5-diglucoside, naringenin-7-O-β-D-glucoside, tannins, catechins, and cyanidin-3-glucoside, betulin, lupeol, lupenone and friedelin.	South	Salmonella Typhimurium (ATCC 14028)	2017	[120]
Acacia mearnsii De Wild., Aloe arborescens Mill., A. striata Haw., Cyathula uncinulata (Schrad.) Schinz, Eucomis autumnalis (Mill.) Chitt., E. comosa (Houtt.) Wehrh., Hermbstaedtia odorata (Burch. ex Moq.) T.Cooke, Hydnora africana Thunb, Hypoxis latifolia Wight, Pelargonium	Plant	acetone extract	bark, leaves, bulb, tuber, root and corms	quercetin-3-O-a-l- arabinopyranoside (<i>P.</i> <i>guajava</i>)	South Africa	Salmonella Isangi, Salmonella Typhi, Salmonella Typhimurium	2017	[121]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
sidoides DC, Psidium guajava L and Schizocarphus nervosus (Burch.) van der Merwe								
Holarrhena floribunda	Plant	ethanolic and methanolic extracts	leaves	Alkaloids	Togo	Salmonella Typhi (clinical strains)	2017	[122]
Zanthoxylum caribaeum Lam.	Plant	ethanolic, methanolic, hexanic, acetone, dichloromethanic, ethylacetate and aqueous extracts	leaves	Germacrene-D, a-Panasinsene and b-Selinene	Brazil	Salmonella enterica	2017	[123]
Rosmarinus officinalis	Plant	essential oil	not specified	not specified	Iran	Salmonella Typhimurium (PTCC 1609)	2017	[124]
Myristica fragans		aqueous extracts	seed	methane, oxybis	India	Salmonella Typhi	2017	[125]
Cajanus cajan (Gandul)	Plant	methanolic extract	leaves	flavonoids, phenolics, and steroids (naringenin)	Indonesia	Salmonella Thypi	2017	[126]
Vitex doniana	Plant	aqueous and methanolic extracts	stem-bark and leaves	phytochemicals alkaloid, saponin, tannin, anthraquinone, flavonoid, phenols, terpenoid andglycoside	Nigeria	Salmonella Typhi	2017	[127]
Hibiscus sabdariffa	Plant	aqueous water	flower calyx	not specified	Mexico	Salmonella Typhimurium and Typhi	2017	[128]
Ziziphora clinopodioides	Plant	essential oil	leaves	nisin	Iran	Salmonella Typhimurium (ATCC 14028)	2017	[129]
Tinospora cordifolia	Plant	aqueous and methanolic extracts	stem	not specified	India	S. Typhimurium (ATCC 23564)	2017	[130]
Sonchus arvensis L. (tempuyung)	Plant	ethanol extracts	leaves	flavonoids and triterpenoids	Indonesia	Salmonella Typhi	2016	[131]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Heliotropium filifolium (Miers) Reiche and of Heliotropium sinuatum (Miers)	Plant	resinous exudate (CH2Cl2) and hexane-ethyl acetate step gradient	fresh parts (cuticular components)	(Filifolinol) (naringenin, 3-O- methylgalanginand pinocembrin)	Chile	Salmonella Typhimurium (ATCC 14028)	2016	[132]
Punica granatum, oak, Thymus vulgaris and Cinnamomum zeylanicum	Plant	ethanolic and chloroformic extracts	peel, oak trunk, thyme fruit and cortex	gallocatechins, delphinidin, cyanidin, gallicacid, ellagic acid, pelargonidin and sitosterol; hymol, carvacrol and flavonoids; cynamaldheide; (4,5-Di-ogalloyl (+) -protoquercitol) and compound III (3,5-Di-ogalloyl (+)-protoquercito	Iraq	Salmonella Typhimurium (chicken isolate)	2016	[133]
Scutellariae radix	Plant	ethanol extracts followed by petroleum ether (PEF), chloroform (CF), ethyl acetate (EAF) and n-butanol (BF)	root	baicalin, wogonoside, baicalein and wogonin	China	Salmonella Typhimurium (CMCC 50041)	2016	[134]
Rhus typhina and Achillea sintenisii	Plant	not specified	aerial and root parts	not specified	Portugal	Salmonella Typhimurium LT2	2016	[135]
Holarrhena antidysentrica (Ha) and Andrographis paniculata (Ap)	Plant	hydroethanolic extract	leaves and stem	alkaloids, flavonoids, saponin, terpenes, phenols, tannins, glycosides carotenoids, anthraquinones, reducing sugars, phlobatannins, sterols	India	Salmonella Typhimurium (MTCC 733)	2016	[136]
Black tea (Kombucha)	Plant	Infusion/fermentation	leaves	Catechin and isorhamnetin	India	Salmonella Typhimurium (NCT 572)	2016	[137]
Curcuma longa	Plant	96% ethanol/essential oil	rhizomes	saponin, tannins, alkaloids and flavonoids (probably curcumin and derivatives)	Colombia	Salmonella spp. (nosocomial isolates)	2016	[138]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Harungana madagascariensis	Plant	aqueous infusion	leaves	not specified	Cameroon	Salmonella Typhimurium	2016	[139]
Piper retrofractum, Phyllanthus emblica, Terminalia chebula, Terminalia bellirica, Piper sarmentosum, Plumbago indica, Piper leptostachyum, Piper nigrum, Zingiber officinale, Piper betle, Garcinia mangostana and Caesal piniasappan	Plant	95% ethanol	fruits, root, stem, rhizome, leaves husk, peduncle and wood	Plumbagin, Piperine, Eugenol, Myristicin, Gingerol, Shogaol and Brazilin	Thailand	Salmonella spp. (piglet isolates)	2016	[140]
Punica granatum	Plant	ethanolic extracts and peel flour	peel, seeds	ellagic acid or ellagic acid derivatives, ellagitannins and HHDP-gallagyl-hexoside	Spain	Salmonella Anatum, Salmonella Typhimurium	2016	[141]
Abrus precatorius L.	Planta	aqueous extracts	leaves, seed and root	steroids, saponins, phenolics, tannins, flavonoids, terpenoids and alkaloids	Nigeria	Salmonella Typhi	2016	[142]
Piliostigma thonningii	Plant	hexane and aqueous extracts	leaves	Tannins, terpenoids, flavonoids, alkaloids, steroids and phenols	Nigeria	Salmonella Typhi	2015	[143]
Baillonella toxisperma	Plant	ethyl acetate, acetone, methanol and hydro-ethanol mixture (2: 8) extracts	leaves and stem bark	terpenoids, tannins, flavonoids, phenols, saponins, steroids and cardiac glycosides.	Cameroon	Salmonella Typhi	2015	[144]
Wood vinegar	Plant	vinegar	natural vinegar	not specified (probably pH 4.15–4.59)	Thailand	Salmonella Enteritidis (DMST15676) Salmonella Typhimurium (DMST17242)	2015	[145]
Aristolochia indica, Carica papaya, <i>Eclipta alba</i> and <i>Phyllanthus amarus</i>	Plant	methanol extracts	leaves	n-Hexadecanoic acid	India	Salmonella Typhi (clinical isolate)	2015	[146]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Curry: Capsicum annuum, Citrus hystrix, Cuminum cyminum L., Allium ascalonicum L., Allium sativum, Cybopogon citratus, Alpinia galangal, ando coconut milk	Plant	water, UHT coconut milk, and fresh coconut milk were used as extractants. Also ethanolic and aquous extracts (Garlic)	fruit, leaves and peel	not specified	Thailand	Salmonella Enteritidis	2015	[147]
Portulaca oleracea	Plant	ethanol extracts	leaves	probably quercetin	Thailand	Salmonella Typhi	2015	[148]
Eucalyptus, mint, cinnamon, garlic, thymus	Plant	oil	bark and leaves	probably cinnamaldehide/ thymol	Egypt	Salmonella Enteritidis, Salmonella Charity and Salmonella Remiremont (chicken isolates)	2015	[149]
Piper crocatum (Red betel vine)	Plant	70% ethanol, followed by n- hexane, ethyl acetate, chloroform and methanol	leaves	saponin and flavonoids	Indonesia	Salmonella Typhi	2015	[150]
Dionisya revoluta	Plant	methanol extracts	aerial parts	not specified	Iran	Salmonella Enteritidis	2015	[151]
Achyranthes aspera	Plant	methanolic extracts followed by chloroform, n-hexane, n- butanol, ethyl acetate and water	leaves	Phenolic compounds, oils, saponins, flavonoids, alkaloids and tannins	Pakistan	Salmonella Typhi (ATCC 19430)	2015	[152]
Alocasia brisbanensis, Canavalia rosea, Corymbia intermedia, Hibbertia scandens, Ipomoea brasiliensis, Lophostemon suaveolens, Syncarpia glomulifera, Smilax australis and Smilax glyciphylla	Plant	hydro-ethanolic (80%) and aqueous extracts	not specified	L. suaveolens leaves: α-pinene, β-caryophyllene, aromadendrene, globulol and spathulenol; S. glomulifera: α-pinene, aromadendrene and globulol; S. glomulifera leaves wax: eucalyptin and S. glomulifera bark: betulinic acid, oleanolic acid-3-acetate and ursolic acid-3-acetate.	Australia	Salmonella typhimurium— Group B (clinical isolate)	2015	[153]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Citrus sinensis	Plant	ethanol, methanol, chloroform, and diethyl ether	peel	saponins, terpenoids, slkaloids, flavonoids, tannins and cardiac glycosides	Pakistan	Salmonella Typhimurium (isolated from spoiled fish)	2015	[154]
Nigella sativa	Plant	essential oil	seed	thymoquinone, p-cymene, a- phellandrene, a-pinene, b- pinen, cis-carveol, trans- anethole, thymol, alongipinene and longifolene	Arabia and India	Salmonella Paratyphi A, Salmonella Enteritidis, Salmonella Typhimurium, Salmonella Heidelberg, Salmonella Agona, Salmonella bongori	2015	[155]
Allium sativum L.	Plant	aqueous extracts	bulb	not specified	South Korea	Salmonella Typhimurium	2015	[156
Spirulina platensis	Plant (algae)	ethanolic and chloroform extracts	cell extracts	not specified	Bangladesh	Salmonella Typhi and Salmonella Paratyphi	2015	[157
Curri = Capsicum annuum, Citrus hystrix, Cuminum cyminum L., Allium ascalonicum L., Allium sativum, Cybopogon citratus, Alpinia galangal, ando coconut milk	Plant	not specified	fruit, peel, seed, bulb, stem, rhizome	especificados por compuesto, reportes previos	Thailand	Salmonella Typhimurium (DT104b)	2015	[158
Vitex doniana	Plant	ethanolic and Acetone extracts	leave, stem bark and root	tannin, saponins, flavonoid, carbohydrate, glycoside, protein and steroid	Nigeria	Salmonella Typhi	2015	[159
Polygonum odoratum	Plant	essential oil	leaves	Dodecanal 55.49%, Decanal 11.57%, Pentacosane 7.26%, p-Anis aldehyde 6.35% mainly	Thailand	Salmonella choleraesuis subsp. choleraesuis (ATCC 35640)	2015	[160
Kelussia odoratissima	Plant	aqueous and ethanolic extracts	leaves	not specified	Iran	Salmonella typhimurium (ATCC 14028)	2014	[161

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Coptidis rhizoma (CR), Houttuyniae herba, Taraxaci herba, Glycyrrhizae radix, Puerariae radix, and Rhizoma dioscoreae	Plant	aqueous infusion	herbs	berberine, ginsenoside Rb1, and glycyrrhizin	China	Salmonella Typhimurium (ATCC 6994) and ST21 (pig carrier)	2014	[162]
Nymphea tetragona	Plant	50% methanol followed by dichloromethane, ethyl acetate, and butanol	body and root	DFNTE: hydrocarbons (46.46%); EFNTE: methyl gallate (70.44%), 1, 2, 3-benzenetriol or pyrogallol (20.61%), and 6, 8-dimethylbenzocyclooctene (5.90%); BFNTE: 2-hydrazinoquinoline (57.61%), pyro-gallol (20.09%), and methyl gallate (12.77%)	Korea	Salmonella Typhimurium (QC strain KTCC2515 and clinical isolates ST171, ST482, ST688, and ST21)	2014	[163]
Virgin coconut oil and palm kernel oil	Plant	essential oil	fruit and seed	not specified	Indonesia	Salmonella Typhi (ATCC 786)	2014	[164]
Virgin Coconut Oil	Plant	oil	fruit	not specified	Indonesia	Salmonella Typhi (ATCC 00786) and Salmonella Typhimurium (ATCC 14028)	2014	[165]
Piper nigrum L.	Plant	ethanolic extracts and chloroform extracts	fruit and seed	tannins, alkaloids and Cardiac glycosides, and tannins, alkaloids and flavonoids	India	Salmonella Typhi	2014	[166]
Morus alba var. Alba, Morus alba var. Rosa and Morus rubra	Plant	hydromethanolic and aqueous extracts	leaves and stem	phenolics and flavonoids	Tunisia	Salmonella Typhimurium (ATCC 14028)	2014	[167]
Khaya senegalensis	Plant	ethanolic, methanolic and aquous extracts	stem bark	saponins, tannins, reducing sugar, aldehyde, phlobatannins, flavonoids, terpenoids, alkaloids, cardiac glycoside and anthroquinones	Nigeria	Salmonella Typhi	2014	[168]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Mentha longifolia	Plant	Ethanolic extracts	leaves	not specified	Iran	Salmonella Typhimurium	2014	[169]
Palm oil (Sania), Virgen coconut oil (Palem Mustika) and soybean oil (Mama Suka)	Plant	oils	seeds and fruits	not specified	Indonesia	Salmonella Typhi (ATCC 19943)	2014	[170]
Heliotropium	Plant	methanolic extract, 2nd extraction with petroleum ether, ethylacetate and chloroform and aqueous	aerial parts	not specified	Iran	Salmonella Enteritidis (ATCC 13311)	2014	[171]
Woad, heartleaf houttuynia herb, baical skullcap, coptidis, andrographitis,	Plant	aqueos extract	bark, leaves, root, rhizome and fruit	not specified	China	Salmonella Typhimurium	2013	[172]
K. senegalensis bark and leaves, S. alexandrina leaves, S. argel leaves, T. indica L. fruits and T. foenum, graecum seeds	Plant	methanolic extract	bark, leaves and seed	not specified	Sudan	Salmonella Typhi (ATCC19430) and Salmonella Paratyphyphi-A (ATCC 9150 / SARb42)	2013	[173]
Phylanthus amarus	Plant	aqueous and ethanolic extracts	leaves	Phyllanthin, Nirtetralin, Linalool, phytol	India	Salmonella Typhi	2013	[174]
Carissa opaca	Plant	95% methanol followed by n- hexane, ethyl acetate, chloroform, butanol and water	fruits	orientin, isoquercetin, myricetin and apigenin (and probably other secondary metabolites)	Pakistan	Salmonella typhy (ATCC 0650)	2013	[175]
Mangifera indica	Plant	acetone extract	leaves	mangiferin	Pakistan	Salmonella Typhi (clinical isolates) and Salmonella (ATCC 14028)	2013	[176
Sinapis alba L.	Plant	essential oil	seeds	4-hydroxybenzyl isothiocyanate	USA	Salmonella spp. (isolates) Salmonella Typhimurium (ATCC 14028), Salmonella Abaetuba and Salmonella Dessau	2013	[177]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Origanum vulgare	Plant	essential oil	seed	not specified	USA	Salmonella Newport (LAJ160311)	2013	[178]
Annona comosus and Citrus senensis	Plant	ethanolic extract	peel	alkaloids, flavonoids, saponins, tannins	Nigeria	Salmonella paratyphi-B, and Salmonella Typhi	2013	[179]
Carthamus nctoricus L., Poncirus trifollata Raf., Scutellaria balcalensis Georgi, Prunus sargentii, <i>Cucurbita</i> moschata, Allium cepa L., Portulaca oleracea L., Xanthium strumarium L., Duchesnea chrysantha, Cudrania tricuspidata and Juniperus chinensis	Plant	ethanolic extract	leaves, peel	not specified	Korea	Salmonella Gallinarum	2013	[180]
Herba pogostemonis	Plant	aqueous extract	leaves	acetol,D-sphignosin, 5- aminoimidazole-1- carboxyamie, caffeic acid, chlorogenic acid, neohesperedin,O- acetylsalicylic acid, quinic acid,3,4-dihydroxybenzoic acid, andDL- hydroxyphenylglycol	Korea	Salmonella Typhimurium (ATCC140)	2012	[181]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Enicostemma littorale	Plant	chloroform, methanol and acetone by soxhlet apparatus	leaves, stem and root	not specified	India	Salmonella Typhi	2012	[182]
Hibiscus rosa-sinensis	Plant	aqueous and ethanolic extracts	flower extract	cyanidin, quercetin, hentriacontane, calcium oxalate, thiamine, riboflavin, niacin and ascorbic acids	India	Salmonella spp.	2012	[183]
Capsicum annuum and Capsicum frutescens	Plant	aqueous and methanolic extracts	fruit	alkaloids, flavonoids, polyphenols, and sterols	Ivory Coast	Salmonella Typhimurium (ATCC 13311)	2012	[184]
Coriandrum sativam (L.)	Plant	essential oil	fruit dry	Bicycle(4.1.0),heptanes,3,7,7- trimethyl-(1a,6a,3a), propanoic acid,2-methyl-3,7- dimethyl octadiennyl ester, (E)-, 2- undecenal, 2- Napthalenemethanol, decahydro-a,a,4a-trimethyl-8- methylene- [2R-(2a,4aa,8aa)]	India	Salmonella Typhi	2012	[185]
Berberis baluchistanica, Seriphidium quettense, Iphionaaucheri, Ferula costata	Plant	crude methanol extracts	roots, aerial parts	not specified	Pakistan	Salmonella Typhimurium	2012	[186]
Oenothera rosea	Plant	aqueous and ethanolic extracts	aerial parts	not specified	Mexico	Salmonella Enteritidis (clinical isolate)	2012	[187]
Ocimum gratissimum and Gongronema latifolium	Plant	aqueous and ethanolic extracts	leaves and stem	not specified	Nigeria	Salmonella Typhi	2012	[188]
Curry: Capsicum annuum, Citrus hystrix, Cuminum cyminum L., Allium ascalonicum L., Allium sativum, Cybopogon citratus,	Plant	Kaeng Kathi (UHT coconut milk	fruit, peel, seed, bulb, stem, rhizome	not specified	Indonesia	Salmonella Typhimurium U302 (DT104b)	2012	[189]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Alpinia galangal, ando coconut milk								
Averrhoa bilimbi Linn	Plant	ethanolic extract	leaves	not specified	Indonesia	Salmonella Typhi	2012	[190
Ocimum gratissimum	Plant	ethanol extracts	leaves	alkaloids, cardiac glycosides, saponins, tannins and steroids	Nigeria	Salmonella Typhi (clinical isolates)	2011	[191]
Ardisia elliptica Thumb	Plant	95% ethanol	fruit	anythocyanins and syringic acid	Thailand	Salmonella sp.	2011	[192
Quercus	Plant	ethanol by soxhlet apparatus	acorn	not specified	Iran	Salmonella Typhi (MDR)	2011	[193
Sonchus spp. (6 sp) <i>S. arvensis</i> , <i>S. oleraceus</i> , <i>S. L</i> ingianus, <i>S. Brachyotus</i> , <i>S. asper</i> , <i>S. uliginosus</i>	Plant	methanolic extract	aerial parts	phenols and flavonoids	China	Salmonella enterica	2011	[194
York cabbage, Brussels sprouts, broccoli and white cabbage	Plant	methanolic extract	whole plant	Hydroxybenzoic acid, hydroxycinnamic acid, flavone, polymethoxylated flavone, glycosylated flavonoid and anthocyanin	Ireland	Salmonella Abony (NCTC 6017)	2011	[195]
Achyrocline satureioides	Plant	ethanolic extract	aerial parts	23-methyl-6- Odesmethylauricepyrone	Argentina	Salmonella Enteritidis	2011	[196
Trapa bispinosa Roxb	Plant	methanolic extract	fruit	not specified	Bangladesh	Salmonella Typhi	2011	[197
Acalypha indica	Plant	methanolic extract	leaves and roots	not specified	India	Salmonella Typhi	2011	[198
Punica granatum	Plant	ethanolic extract	peel	not specified	Korea	Salmonella Typhi (ATCC 19943), S. Dublin (ATCC 39184), S. Derby (ATCC 6960), S. choleraesuis (ATCC 7001) y S. Gallinarum (ATCC 9184), S. Enteritidis, S.	2011	[199

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
						Typhimurium, S. Gallinarum y S. Paratyphi A		
Punica granatum L Eugenia jambolana Lam., Eugenia uniflora L., Caryophyllus aromaticus L., Psidium araca Raddi, Achyrocline satureioides (Lam.), Rosmarinus officinalis L., Cynara scolymus L., Salvia officinalis L., Laurus nobilis L., Bidens pilosa L., Baccharis trimera (Less.) DC, Plectranthus barbatus Andrews, Sonchus oleraceus L., Mikania glomerata Spreng., Taraxacum officinale F.H. Wigg, Emiia sonchifolia (L) DC, Plantago australis Lam., Maytenus ilicifolia (Schrad) Planch, Aloe arborescens Mill., Malva sylvestris L.	Plant	hydromethanolic extracts	leaves, fruit, package content, aerial and flowered aerial portions.	not specified	Brazil	Salmonella Agona, Salmonella Anatum, Salmonella Cerro, CerroCubana, Salmonella Derby, Salmonella Enteritidis, Salmonell Give, Salmonella Heidelberg, Salmonella Infantis, Salmonella London, Salmonella Manhattan, Salmonella Meleagridis, Salmonella Montevideo, Salmonella Newport, Salmonella Oranienburg, Salmonella Panama, Salmonella Pullorum, Salmonella Typhimurium	2011	[200
Cucurbita pepo	Plant	methanolic and ethanolic extracts	seed	saponins, flavonoids, Tannins, alkaloids, and steroids	Nigeria	Salmonella Typhi	2011	[201
Aloe vera	Plant	methanolic and ethanolic extracts	leaves	Anthraquinone, Alkaloids, Saponins, Balsams, Flavonoids and Tannins	Nigeria	Salmonella Typhi	2011	[202
Gynostemma pentaphyllum	Plant	ethanolic extract	leave, stem	not specified	Thailand	Salmonella Typhi Salmonella Typhimurium	2011	[203

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Terminalia stenostachya y Terminaliaspinosa	Plant	dichloromethanic, methanolic, acetone and ethanolic extracts	stem barks and roots	not specified	Tanzania	Salmonella Typhi	2011	[204]
Hofmeisteria schaffneri	Plant	infusion and essential oil	aerial parts	hofmeisterin III, thymyl isovalerate and 8,9-epoxy-10- acetoxythymyl angelate	Mexico	Salmonella Typhi (ATCC9992)	2011	[205]
Ficus polita Vahl.	Plant	methanolic extract	roots	euphol-3- O -cinamato C 39 H 56 O 2, lupeol C 30 H 50 O, taraxar-14-eno C30 H 50 O 1	Cameroon	Salmonella Typhi (ATCC6539)	2011	[206]
Aegle marmelos (L.) Corr. Serr. (Rutaceae), Cassia fistula L., Moringa oleifera Lam., Melia azedarach L., Bombax ceiba L. and Brassica rapa ssp. campestris L.	Plant	aqueous and methanolic extracts	vegetables, seeds	not specified	Pakistan	Salmonella Typhi	2011	[207]
75 plants (Healianthus annum Linn.)	Plant	ethanolic extracts	leaves	not specified	India	Salmonella Typhosa	2010	[208]
Syzygium cumini	Plant	aqueous and ethanolic extracts	leaves	flavonoids, alkaloids,	India	Salmonella Enteritidis, Salmonella Typhi, Salmonella Typhi A,Salmonella paraTyphi A, Salmonella paraTyphiB	2010	[209]
Black pepper (Piper nigrum Linn.)	Plant	acetone extract; dichloromethanic extract;	fruit	piperine	India	Salmonella Typhi	2010	[210]
Abrus precatorius L.	Plant	methanolic and petroleum ether extract	leaves, seeds and roots	Methanolic and petroleum ether extract	India	Salmonella Typhi, Salmonella Paratyphi A, Salmonella Paratyphi B	2010	[211]
Psidium guajava	Plant	methanolic extract	leaves	flavonoids: morin-3- Olyxoside, morin-3-O- arabinoside, quercetin-3- Oarabinoside and quercetin.	Thailand	Salmonella enterica (ATTC 8326)	2010	[212]

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
				Anthocyans, alkaloids, tannins, and terpenoids.				
Origanum vulgare L.	Plant	essential oils	aerial parts	not specified	Turkey	Salmonella Enteritidis RSKK 96046,	2010	[213]
Tectona grandis	Plant	methanolic extract	leaves	not specified	India	Salmonella Typhimurium (MTCC 98	2010	[214]
Ocimum canum, Acalypha indica, Eclipta alba and Lawsonia inermis	Plant	chloroform and methanol	whole plant	not specified	India	Salmonella paraTyphi	2010	[215]
Adiantum capillus-veneris L. (Adiantaceae), Adiantum incisum forsk. (Adiantaceae), Adiantum lunulatum Burm. F. (Adiantaceae), Actiniopteris radiata (Swartz.), Enlace (Actiniopteridaceae), Araiostegia pseudocystopteris Copel. (Davalliaceae), Athyrium pectinatum (Wall ex Mett.) T. Moore (Athyriaceae), Chelienthes albomarginata Clarke (Sinopteridaceae), Cyclosorus dentatus (Forsk.) Ching (Thelypteridaceae), Dryopteris cochleata (Don.) C. Chr. (Dryopteridaceae), hipodematio crenatum (Forsk.) Kuhn (Hypodematiaceae), Marsilea minuta L. (Marsileaceae) y Tectaria coadunata (J. Smith)	Plant	aqueous and methanolic extracts	leaves	not specified	India	Salmonella arizonae (MTCC No. 660), Salmonella Typhi (MTCC No. 734)	2010	[216

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Ecklonia cava	Plant (algae)	EtOH followed by n-hexane, CH2Cl2, EtOAc, n-BuOH (10 g) and aqueous	not specified (probably full algae)	Eckol	Korea	Salmonella Typhi (ATCC 19943), Salmonella Dublin (ATCC 39184), Salmonella Derby (ATCC 6960), Salmonella choleraesuis (ATCC 7001), Salmonella Gallinarum (ATCC 9184), Salmonella Enteritidis, Salmonella Typhimurium, S. Gallinarum, and Salmonella Paratyphi A	2010	[217]
Thymus vulgaris L., Ocimum basilicum L., Coriandrum sativum L., Rosmarinus officinalis L., Salvia officinalis L., Foeniculum vulgare L., Mentha spicata L., Carum carvi L.	Plant	essential oil	not specified	not specified	Romania	Salmonella enterica serovar Enteritidis Cantacuzino CICC10878, Salmonellaenterica serovar Enteritidis	2010	[218]
Pikutbenjakul = <i>Piper longum</i> , Piper sarmentosum, Piper interruptum, Plumbago indica y Zingiber	Plant	ethanolic extract	not specified	not specified	Thailand	Salmonella sp. Salmnella typhy amd salmonella Typhimurium	2010	[219]
Quercus infectoria, <i>Kaempferia</i> galanga, Coptis chinensis and Glycyrrhiza uralensis	Plant	DMSO	galls, roots, rhizomes,	not specified	Thailand	Salmonella Typhi (DMST 5784)	2010	[220]
Eugenol	Plant	essential oil of clove	flower extract	177 peaks and HHDP-gallagyl- hexoside	Indonesia	Salmonella Typhi	2010	[221]
Sida rhombifolia Linn.	Plant	methanolic extract	not especified	polyphenols, alkaloids and steroids	Cameroon	Salmonella Typhi, Salmonella Enteritidis	2010	[222]

Table 4. Summary of frequently reported natural products from plant origin against salmonella.

Parental organism	Origin	Extraction method	Segment used	Bioactive compound(s)	Location	Salmonella serovar	Year	Ref
Goat milk kefir (Lactococcus cremoris, Streptococcus cremoris	Bacteria and Yeast	no extraction	microbial cells	lactic acid, ethanol and CO ₂ , diacetyl acetaldehyde, ethyl and	Indonesia	Salmonella Typhimurium (ATCC 14028)	2019	[223]
Epicoccum nigrum, Entada abyssinica	Fungus and plant	ethyl acetate extract	leaves	not specified	Cameroon	Salmonella Typhimurium	2017	[224]
Origanum vulgare, Lactococcus lactis (Nisin), EDTA	Plant and Bacteria	essential oil	seeds	carvacrol, p-cymene and y-terpinene	Brazil	Salmonella Enteritidis	2016	[225]
Allium sativum, Nigella sativa, Azadirachta indica, Ficus carica, Trigonella foenum-graecum and honey	Plant and Animal	aqueous extracts	bulb, seed, leaves and fruit	not specified	Pakistan	Salmonella spp.	2014	[226]
Apis mellipodae honey and Allium sativum	Animal and plant	macerated and aqueous dilution	honey/bulb	Honey: high, osmolarity, hydrogen peroxidase, acidity and Allium sativum: allicin	Ethiopia	Salmonella Typhi (clinical isolate) and Salmonella spp. (NCTC 8385)	2013	[227]

Table 5.
Summary of reported natural products of combined origins against salmonella.

congress and meeting proceedings where useful data were present. NPs and bioactive principles were registered according to the molecules isolated by the authors and/or in contrast to the literature. This search was not exhaustive, rather, we aim to obtain a random sample of information using the simplest terms on the matter of natural products for salmonellosis.

All these works were developed on all continents, being Asia the most active, followed by Africa, America, Europe and Oceania (**Figure 1A** and **B**). It is noteworthy that much of the research was developed in equatorial locations where biodiversity is abundant. Country-wise, there is a remarkable number of publications from India and Indonesia, where incidence of salmonella is high. The map constructed for the distribution of publishing frequencies, in fact, resulted fairly similar to a previously reported salmonella incidence map (**Figure 1A** versus [9]). The number of articles per year showed an upward trend though it stabilizes in the last five years (**Figure 1C**).

The spectrum of biological activities evaluated are as diverse as the application to which they are oriented, from the study of antimutagenic, antioxidant,

Animal species	Vegetable species	Microorganisms	Solvents	Bioactive compound
Identification of genus and, if possible, species	Geographical site	Identification of genus, and species	Explanation for its selection	Isolation technique
	Harvesting data	Reference strain identification	No- reactivity assessment	Structure determination method (MS–GC, for instance)
	Ethnobiological identification	Identification of origin:	No- interference assessment	
		Identification by PCR	No-toxicity assessment	

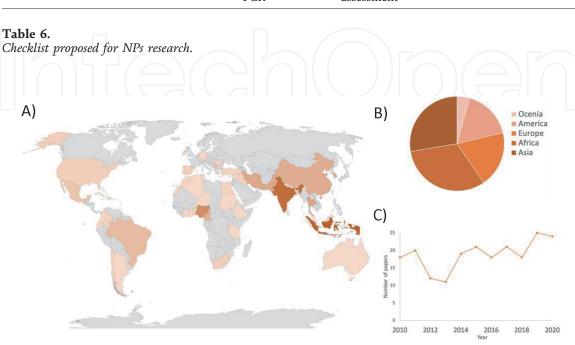


Figure 1.(A) Distribution map of publishing frequencies. (B) Continental frequency. (C) Publications per year.

anticancer, anthelmintic, antiviral, antifungal activities to its antibacterial potential, being its activity against *salmonella* spp. one of the most studied activities.

The analysis of the last decade research render studies exploring the antibacterial activity against *salmonella* serovars of crude extracts and essential oils, from compounds of natural origin, as well as their components. A wide variety of these NPs have been evaluated from commercial formulations, products of animal origin such as honey, propolis, milk and chitosan, through complete plants and/or their components (roots, stem, leaves and flowers), up until products of microbial metabolism as crude protein extracts, membrane and cell wall glycosides, natural antibiotic peptides (nisin). Several chemical compounds such as water, ethanol, methanol, acetone, formaldehyde, hexane, ethyl acetate and chloroform were used as solvents by direct maceration extraction rather than vapor distillation or more complex methods.

Nonetheless, we believe the description of methodological conditions could further standardized with the inclusion of a fixed set of data. According to our observation, the list of items enlisted in **Table 6** could be a minimal checklist when performing NP research.

7. Conclusions

Salmonellosis, caused by *salmonella* serovars, is still an uneradicated disease both in industrialized and developing countries. Multidrug resistance is a phenomenon increasingly widespread and alternative tools for disease control are urgently necessary. Natural products research based on traditional medicine is nowadays a consolidated study field full of vitality, *salmonella* research in particular has an upward trend with work being develop worldwide. Authors cited within this chapter explored biological activities of local organisms for the solution of salmonellosis for their communities, although a minority showed interested in foreign resources or commercial formulations. We observed a higher number of active researches on countries with diverse and abundant natural resources coincidentally also with high salmonellosis incidence. Even though our search is a minimal sample from the whole work being published on NPs and salmonellosis, it reveals certain features of the field.

Most of the works displayed in here are initial screening in vitro studies, maybe due to the scarce number of sources for funding in vivo applications. In perspective, NPs studies for clinical applications is a potential goal in order to control this disease.

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Conflict of interest

Authors declare no conflict of interests.





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