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EMERGING PATHOGENS AND BIOACTIVE MATERIALS: IN GREENING THE 21ST CENTURY BIOMEDICAL SCIENCES

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ABSTRACT

Emerging pathogens are a major threat to the biological safety of the world in the 21st century. Owing to many reasons, the emergence and re-emergence of deadly pathogens have increased and posed a considerable challenge to human and animal health, alike. Various factors including ecological changes along with other specific risk factors related to the type and classification of the pathogen, route of transmission and host range are among the most commonly associated criterion for emerging and re-emerging pathogenic environments. Owing to the lack of essential in-depth knowledge, challenges remain in this domain to tackle and combat emerging pathogens. Significant research efforts, exploitations of natural resources with potent bioactivities, and development of scientific innovations along with new degrees of integration are required to tackle this challenging threat. Aiming to resolve these issues, various methodological approaches including *in-vitro*, *in-vivo*, *ex-vivo*, etc. have been exploited, in the past several years. Research is underway around the globe to develop or engineer bioactive materials. Among them, biomaterials-based therapeutic constructs are of supreme interests in the current biomedical sector. The following measures, i.e. (i) principle sources of emerging pathogens, (ii) linking pathogen surveillance of wild and domestic animals, (iii) public health surveillance at the national and international level, and (iv) importantly the coverage of these surveillance issues, etc. should be taken with utmost care. This will ultimately make a significant and essential contribution to the detection and control of emerging and re-emerging pathogens.

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1 Introduction

The commonly accepted definition of an emerging pathogen is as: “an infectious agent with increasing incidences following its first introduction into a new host population” (Woolhouse & Dye, 2001). Whereas, a re-emerging pathogen can be defined as: “a pathogen whose incidence is increasing in an existing host population as a result of long-term changes in its underlying epidemiology” (Woolhouse & Dye, 2001; Guan & Hoover, 2005). These definitions of emerging and re-emerging pathogens are envisioned to discriminate the short-term, local upsurges in the occurrence that illustrate the epidemiological strategies of many infectious diseases, from the long-term, worldwide tendencies that establish ‘true’ emergence (Woolhouse, 2002). The emerging and re-emerging pathogens/diseases, for example, Zika fever, Ebola virus (Singh et al., 2016; Singh et al., 2017); John’s disease (*Mycobacterium avium* subsp. *paratuberculosis*) (Chaube et al., 2017), listeriosis (*Listeria monocytogenes*), Arcobacters (Ramees et al., 2017); bovine spongiform encephalopathy (BSE) in cattle; phocine distemper in seals, multidrug-resistant *Staphylococcus aureus* (MRSA) and drug-resistant *Plasmodium falciparum*, and others are having an increasing impact on human and animal health, as well as zoonotic concerns (Daszak et al., 2000; Cleaveland et al., 2001; Dobson & Foufopoulos, 2001; Dhama et al., 2013). The rising incidences of emerging antibiotic resistance have also posed a challenge to the health of humans and their companion animals. Broadly speaking MRSA, alone, is responsible for causing deadly infections in man, poultry, and several other animal species. Since, its early discovery in the 1960s, it has been isolated and reported in live poultry birds and their meat products worldwide (Tiwari et al., 2013; Zaheer et al., 2017).

With ever increasing scientific knowledge and social awareness, now the people are more concern about the MRSA issues. Besides MRSA, the emergence of new antimicrobial resistance (AMR) or multidrug resistance (MDR) bacterial strains is posing serious challenge to health care services (Jindal et al., 2015; Holmes et al., 2016; Bilal et al., 2017a; Bilal et al., 2017b; Bilal et al., 2017c; Rasheed et al., 2017). AMR is defined as a temporary and permanent capability of a microbial strain, and its progeny to resist and stay viable and multiply against the medication previously used to treat them. Owing to this notable resistivity and non-susceptibility, microbes have been classified as resistant strains to the concentration of an antimicrobial agent used in practice (Cloete, 2003). The AMR/MDR is a growing problem at the global level. Developing a range of strategies to reduce reliance on antimicrobials will be a key challenge for the future (UK Five Year Antimicrobial Resistance Strategy 2013 to 2018). Owing to the antibiotic resistance, infections now account for 25,000 deaths in Europe alone (European Centre for Disease

Prevention and Control), and about 23,000 deaths and over 2 million illnesses in the US (Centers for Disease Control and Prevention), annually. Owing to the emerging or re-emerging infectious diseases caused by various microorganisms, much attention is now being focused towards alternative and effective approaches to be adopted to control and limit such deadly infections (Tiwari et al., 2013; Dhama et al., 2014a; Dhama et al., 2014b; Prasad et al., 2018; Tiwari et al., 2018). In this context, novel materials with antimicrobial activities are attracting the considerable attention of both academia and industry, especially in the biomedical, and other health-related sectors of the modern world (Iqbal et al., 2014a; Iqbal et al., 2015a; Iqbal et al., 2015b; Bedian et al., 2017). Because of the growing consciousness and demands of legislative authorities, the manufacturer, to reduce bacterial population in healthcare facilities and possibly to cut pathogenic infections, development of novel anti-microbial active materials which are biocompatible and biodegradable are considered to be a potential solution to such a problematic issue.

2 Concerning pathogens – past and present scenarios

Approximately, half a century ago in the 1950s, *Staphylococcus aureus*, *Salmonella*, *Bacillus cereus* and *Clostridium perfringens* were the concerning pathogens transmitted through food or other routes. Also, changes in livestock farming and industrialization of slaughtering of pigs played a significant role. Transportation of live animals for slaughtering has in some studies been proved to be an important factor in the propagation of the bacterium from farm to farm (Nesbakken, 1992; Skovgaard, 2007). Three classes of antibiotic-resistant pathogens are emerging as major threats to public health. Among them, the first class chiefly covered multidrug-resistant *Staphylococcus aureus* (MRSA). Waters et al. (2011) characterized US meat and poultry samples ($n = 136$) for multidrug-resistant *Staphylococcus aureus* prevalence, antibiotic susceptibility profiles, and genotypes. Out of 136 test samples, 47% test samples were found contaminated with *Staphylococcus aureus*, and multidrug resistance was prevalent among 52% isolates. In the same study, authors have reported the prevalence of MRSA in one sample each of beef, turkey, and pork. According to the authors, though the presented data (sampling size) was not sufficient to accurately estimate the MRSA prevalence rates, however, it was consistent with a previous US-based study (Pu et al., 2009). Evidently, based on the literature data, higher MRSA contamination or prevalence rates have been reported among meat and poultry samples in the Netherlands, where ST398 is the dominant food-borne sequence type (De Boer et al., 2009). ST398 alone makes up a considerable proportion of the community-acquired methicillin-resistant *S. aureus* (MRSA) cases in the Netherlands (Van Loo et al., 2007). Several other research investigations have also documented the high-level occurrence of MRSA including ST398 along with intensively raised swine in the

European Union, Canada, and the United States (Khanna et al., 2008; Smith & Pearson, 2011). Likewise, MRSA strains have also been isolated from several food production animals, including pigs, cattle, chicken and other animals (Huijsdens et al., 2006; Lee, 2006; De Neeling et al., 2007), with special reference to pigs and pig farmers (De Boer et al., 2009). Other widespread clonal lineages include caMRSA ST8 (“USA300”) and ST80 in the USA and Europe (Tenover et al., 2006; Tristan et al., 2007; Witte et al., 2007; Kennedy et al., 2008; Cuny et al., 2010).

The second class of emerging pathogens covered most of the Gram-negative bacteria which are less prevalent than MRSA (Fischbach & Walsh, 2009). However, bacteria belong to this class do pose serious infectious threats that are truly untreatable. Major stains include *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. These strains have been found resistant to some or almost all antibiotic classes, e.g., quinolones, tetracyclines, and carbapenems, commonly used to treat Gram-negative bacterial infections (Falagas et al., 2005). The third class of emerging pathogens chiefly comprises on extensively drug-resistant (XDR) bacterial strains. This includes MDR or XDR Mycobacterium tuberculosis, MDR-TB or XDR-TB, respectively. The candidate belongs to this class are a rising threat with some reported cases in the United States and other developing countries (Dorman & Chaisson, 2007; Fischbach & Walsh, 2009).

3 Biomaterials

A biomaterial is defined as a matter or surface that can interact with biological systems to support, replace or repair damaged tissue or a biological function. From the origin viewpoint, it can be natural or synthetic. From the last several years, biomaterials have gained special research interests as novel candidates and alternatives to the traditional petroleum-based synthetic counterparts (Iqbal et al., 2013; Iqbal, 2015).

3.1 Potentialities and opportunities

Many research efforts have been made to engineer new types of high-performance materials-based constructs (Iqbal et al., 2014b; Iqbal et al., 2016a; Iqbal et al., 2016b; Iqbal et al., 2016c; Bedian et al., 2017). This area is moving towards the development of ‘greener’ technologies and in turn, the principle of ‘going green’ has directed this search towards eco-friendly materials. The fact is that environmental legislation is the driving force behind the development of these materials (Iqbal, 2015). With ever-increasing scientific research, knowledge and socioeconomic awareness, industrial communities are now more concerned about the environmental impact of persistent plastic-based wastes. Moreover, the disposal methods are limited and no longer acceptable. The divergence from synthetic materials to bio-based

biomaterials is becoming the center of interest for industrial communities around the globe. On the other hand, biopolymers have some advantages over petroleum-based polymers, such as being renewable, abundant and biodegradable while also providing competitive mechanical properties. So, the focus has been shifted to polymers originating from bio-based renewable sources, which are often biocompatible and biodegradable (Plackett et al., 2003). Therefore, in this context, bio-based composite materials are being engineered for target applications in different sectors of the modern world.

In this perspective, there is an urgent need for the development of materials that would not involve the use of the toxic or noxious component and potentially be resistive against the wider community of various microbes to avoid some serious wound contaminations (Iqbal et al., 2015c; Iqbal et al., 2015d). One area that has received limited attention so far, but that will gain in importance as naturally conferring antimicrobial agents use becomes further established, is the incorporation of such novel agents into the materials to provide an antibacterial effect on contact of that material with the target bacterium. Such antimicrobial active biomaterials might have great potential to respond to a new infection before the clinical signs are evident, with the potential to significantly improve patient prognosis. Antimicrobial agents-impregnated materials could be used as medical implants and in applications relevant to hospital hygiene. However, there are also clear industrial and biotechnological requests for materials that are loaded with natural agents that can quickly prevent deleterious microbial action following contamination events. It is intended that a technology platform for future exploitation, e.g., *in vivo* and *ex vivo* designs to find out other suitable potential applications such as biomedical implants of these newly developed novel materials, could also be established.

3.2 Major limitations of Biomaterials

Besides several advantages, biomaterials also have numerous disadvantages subject to their type, structure, and nature. The ever increasing consumption and reliance on synthetic-based biomaterials have raised serious environmental and human health concerns. On the other hand, the major limitations, yet to overcome, of natural-based biomaterials includes their tendency for calcification and eventual bio-deterioration. Among several metals, gold, silver, stainless steel, nickel-titanium alloy, and cobalt-chromium alloy are the most commonly used biomaterials (Bilal et al. 2017b; Rasheed et al. 2017). In spite of this wide spread usage of metals, the corrosion of metal is main disadvantage which happens due to chemical reaction with the body enzymes and acids. It also can cause metal ion toxicity in the body. The leaching behavior which ultimately leads to wear and

tear limit natural polymers. Other major limitations include low mechanical stability, degradability, insolubility in the common solvents generally available, low/high biocompatibility, immunological reaction, possible rejection by host, corrosion, high level natural variability, lack of consistency, and difficulties in processing and fabrication, etc. which varies subject to the type and classification of biomaterials (Iqbal, 2015).

4 Applications of biomaterials

The biomaterials exploitation for biotechnological applications at large and biomedical in particular has several intrinsic advantages that include biocompatibility, biodegradability, renewability, sustainability, and non-toxicity (Iqbal 2015; Gallegos et al., 2016). The sustainability concept is shown in Figure 1. From the application viewpoint, a wider spectrum of biomaterials and biomaterials-based novel constructs has been engineered for target applications with a particular reference to the active antimicrobial constructs (Iqbal, 2015). Figure 2 illustrates various biomedical applications of bacterial cellulose as a model example from bio-based biomaterials. Some examples include collagen, PLA, and chitosan. All these materials are well characterized and developed into value-added structures, thus can provide a proper route to emulate bio-systems - a biomimetic approach.

4.1 Antimicrobial active materials

Bio-based biomaterials are moving into the mainstream applications changing the dynamics of 21st-century materials and their utilization in drug delivery strategies. Owing to the increasing consciousness and demands to reduce bacterial contaminations in healthcare facilities and possibly to cut pathogenic infections, the engineering aspects of novel active anti-microbial materials are considered to be a potential solution to such a problematic issue (Iqbal, 2015). These materials have not only been a motivating factor for the materials scientists, but also they provide potential opportunities for improving the living standard (Nair & Laurencin 2007; Iqbal, 2015). Research is underway, around the globe, to develop materials-based novel constructs with antibacterial potentialities (Michl et al., 2014; Wang et al., 2014; Iqbal et al., 2015b; Lu et al., 2015). For instance, recently, Bilal et al. (2017b) biosynthesized silver nanoparticles (AgNPs) and AgNPs-loaded chitosan-alginate constructs with significant antibacterial activities against six bacterial strains, i.e. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Morganella morganii* and *Haemophilus influenza* (Bilal et al., 2017b). However, excess release of silver nanoparticles inhibits osteoblasts growth and can also cause many severe side effects such as cytotoxicity (Wang et al., 2014). Therefore, there is a persistent need to prepare green composites using one or more individual biopolymers to reduce or even eliminate the risk of

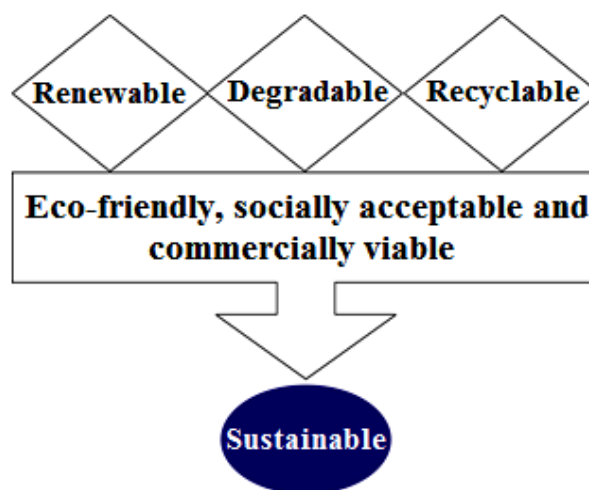


Figure 1 Concept of “sustainability” (Reproduced with permission from Iqbal, 2015; Gallegos et al., 2016).

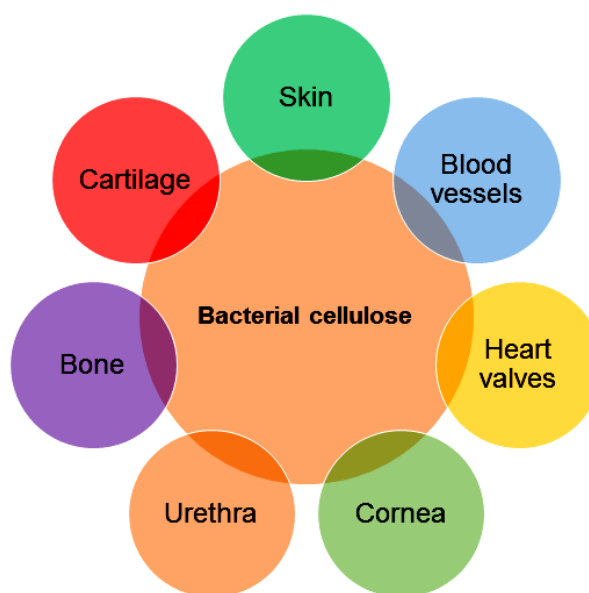


Figure 2 Prospects for the various biomedical applications of BC and BC-based materials (Reproduced with permission from Gallegos et al., 2016).

bacterial infection without impairing the cytotoxicity capabilities. The antibacterial potential of natural phenols, along with their antiseptic characteristics, has already been reported elsewhere (Ultee et al., 2002; Rukmani & Sundrarajan, 2012; Shahidi et al., 2014). Research on several proteins, including collagen, fibroin, keratin, and others are in progress for the development of materials with multifunctional characteristics. Among the natural materials, keratinous proteins are attractive candidates to prepare keratin-based composites which in turn may find potential

applications in biomedical, pharmaceutical, tissue engineering, and cosmetic industries (Khosla & Ullah, 2013). By this evidence, we hypothesized that natural phenols are among the practical choice for inhibiting bacterial infections and investigated the antibacterial features of these compounds, incorporated materials. Figure 3 illustrates a development and antibacterial behavior of phenol-g-keratin-EC based materials (Iqbal et al., 2015a).

The antibacterial mechanism of natural phenols is naturally concomitant due to the presence of active hydroxyl groups. This is because the interaction between natural phenols and bacteria can change the metabolic activity of bacteria and eventually cause their death (Iqbal et al., 2015a; Iqbal et al., 2015b; Iqbal et al., 2015c). Based on an earlier published data, most of the phenolic compounds including gallic acid, *p*-4-hydroxybenzoic acid, and thymol have an ability to disrupt the lipid structure of the bacterial cell wall, further leading to a destruction of the cell membrane, cytoplasmic leakage, and cell lysis which ultimately leads towards the cell death (Veras et al., 2012; Milovanovic et al., 2013; Shahidi et al., 2014). Furthermore, the delocalization of the electrons on their structure has also been reported to contribute to their antibacterial activity as well (Ultee et al., 2002; Elegir et al., 2008).

4.2 Biomaterials based biocomposites

There has been increasing research interest in the development of biomaterials-based bio-composites with multi-characteristics, i.e. (1) stronger, (2) stiffer, (3) lighter along with other multi-functional properties for a variety of industrial and biotechnological applications (Iqbal, 2015). A composite is defined as a “material that consists of two or more distinct materials/polymers in order to obtain tailor-made characteristics or to improve or impart ideal properties”. More importantly, tailor-made characteristics include but not limited to the specific strength, thermal properties, surface properties, biocompatibility, and biodegradability features that the individual material fails to demonstrate on its own (Iqbal et al., 2015d; Iqbal et al., 2016a). Whereas, a biocomposite can be defined as “composite materials derived from a biological origin and comprise on one or more phases are termed as bio-composites” (Fowler et al., 2006). A broad definition of a bio-composite is a composite material made up of natural or bio-derived polymers, *e.g.*, BC/MC, PHAs, and PLA (Iqbal, 2015). So far, a range of methodologies has been successfully adopted for the production of BC and BC-based composites (Iqbal, 2015). Furthermore, potential applications of BC and BC-based composites are also provided in Table 1. In recent years, cellulose-based materials have been widely employed in the area of infection-free wound healing, tissue engineering/implants applications. Naturally occurring phenol grafted P(3HB)-EC bio-composites, on the other hand, are

expected to exhibit excellent HaCaT compatibility and potentially favorable for cell proliferation.

Recently, Iqbal et al. (2015a) have developed a series of novel bio-composites with natural phenols as functional entities and P(3HB)-EC as a base material using laccase as a grafting tool. *In vitro* biocompatibility of CA-g-P(3HB)-EC composites i.e., 0CA-g-P(3HB)-EC (control composite); 5CA-g-P(3HB)-EC; 10CA-g-P(3HB)-EC; 15CA-g-P(3HB)-EC and 20CA-g-P(3HB)-EC was achieved with the human keratinocytes-like HaCaT cells (Iqbal 2015; Iqbal et al., 2015b). Additionally, the morphologies of cell cultured from all of the test composites displayed healthy shape at 5 days, nevertheless, the amount of HaCaT cells seeded on the surface of 15CA-g-P(3HB)-EC composite was higher than those of 20CA-g-P(3HB)-EC composite (Figure 4), which is again consistent with the results from viability/cytotoxicity analysis (Figure 5).

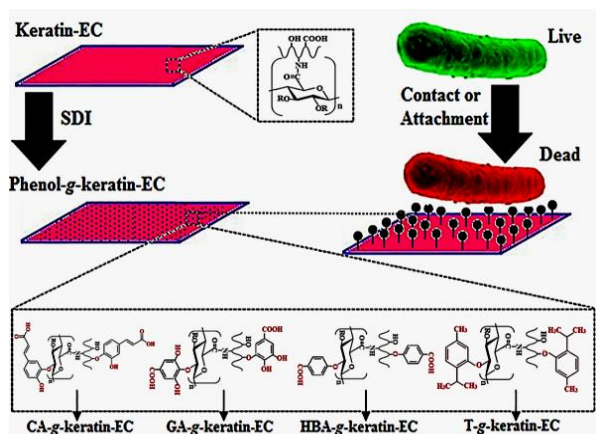


Figure 3 The design and antibacterial behavior of phenol-g-keratin-EC based materials (Reproduced from Iqbal et al., 2015a, with permission from The Royal Society of Chemistry).

5 Concluding remarks and future considerations

Through sophisticated design and novel characteristics, the material can be modified to achieve an optimal infective capability. Such materials include but not limited to the biodegradable and biocompatible films and highly porous 3-D constructs. Bio-based biomaterials are versatile to synthesize novel constructs with multifunctional characteristics for potential applications in the biomedical sector. A novel type of potent materials could be designed for the management and skin regeneration/repair from injury, particularly burns and ulcers, where the risk of bacterial infection is high. Material structure and performance integrity need to be accessed using a range of analytical and imaging techniques. Considering this scenario, research, production, and commercialization of such novel

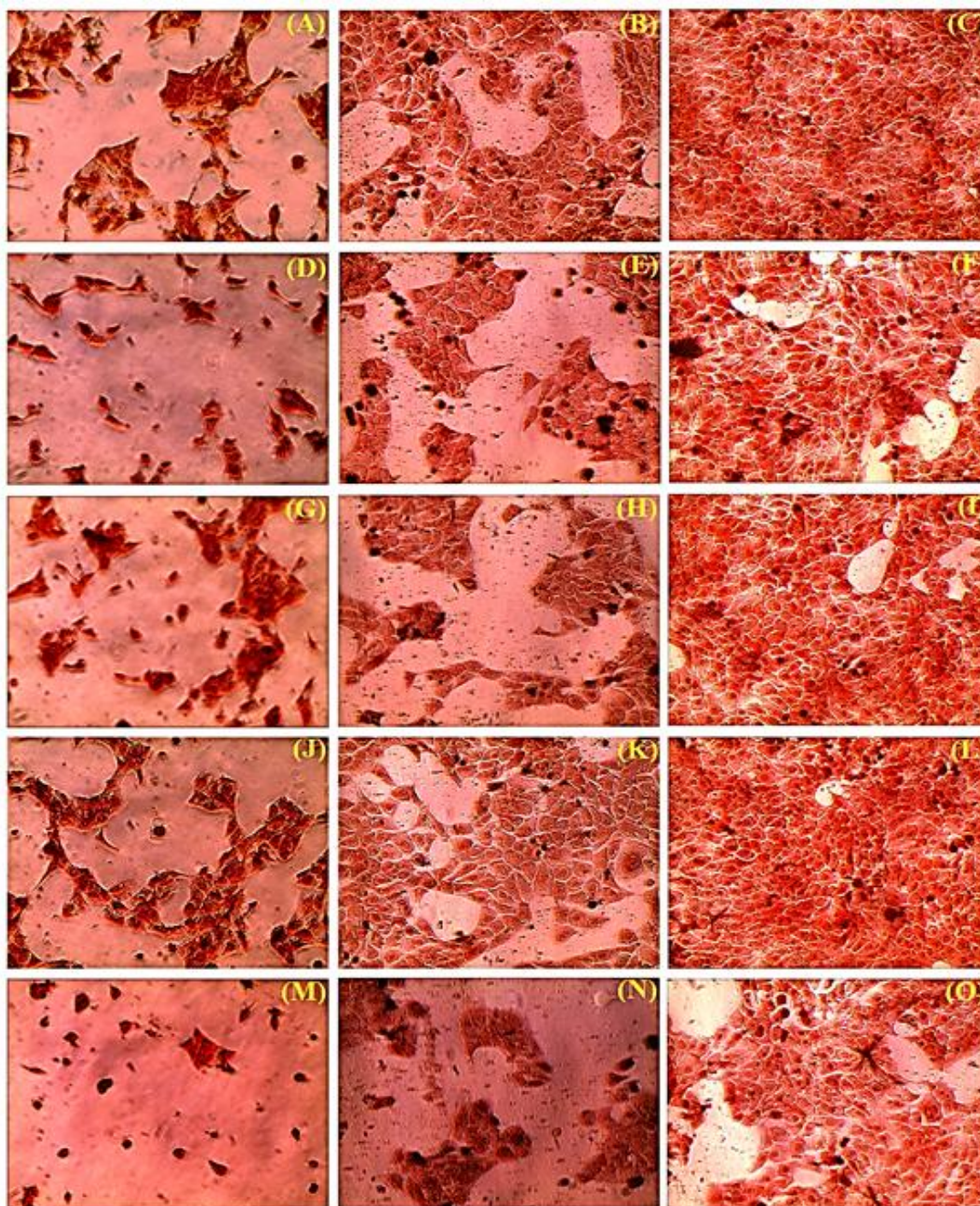


Figure 4 Adherent morphology of stained images of human keratinocytes-like HaCaT cells seeded onto the composite surfaces. Images A, B, and C represent the HaCaT cells on native P(3HB)-EC composite (i.e., 0CA-g-P(3HB)-EC) after 1, 3 and 5 days of incubation, respectively; images D, E, and F represent the adhered HaCaT cells on 5CA-g-P(3HB)-EC composite after 1, 3 and 5 days of incubation, respectively; images G, H and I represent the adhered HaCaT cells on 10CA-g-P(3HB)-EC composite after 1, 3 and 5 days of incubation, respectively; images J, K, and L, represent the adhered HaCaT cells on 15CA-g-P(3HB)-EC composite after 1, 3 and 5 days of incubation, respectively and images M, N and O represent the adhered HaCaT cells on 20CA-g-P(3HB)-EC composite after 1, 3 and 5 days of incubation, respectively. All of the test samples were stained using neutral red dye (5 mg/mL) for 1 h followed by three consecutive washings with PBS at an ambient temperature. All images were taken at 100X magnification (Reproduced with permission from Iqbal, 2015; Iqbal et al., 2015e).

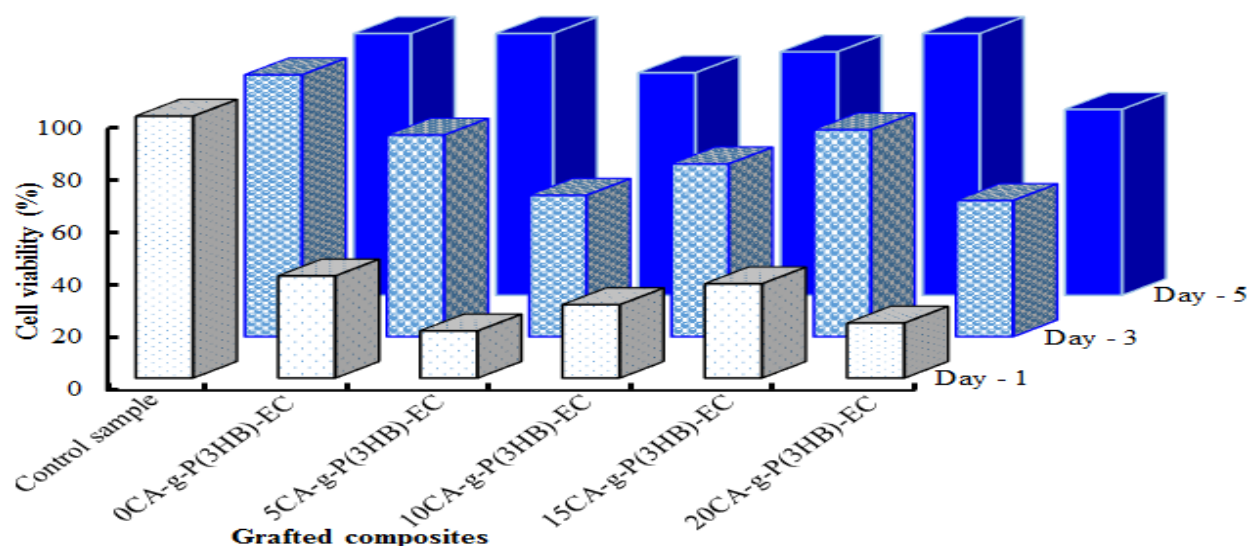


Figure 5 Neutral red dye concentration-dependent percentage cell viability of human keratinocytes-like HaCaT cells after 1, 3 and 5 days of incubation onto the CA-g-P(3HB)-EC composite surfaces (mean \pm SD, n = 3) (Reproduced with permission from Iqbal, 2015; Iqbal et al., 2015e).

Table 1 Potential/Proposed Applications of Some Bacterial Cellulose-based “Green” Composite Materials (Reproduced with permission from Gallegos et al., 2016).

BC-based Materials	Methodology	New/improved functionalities	Potential/Proposed Applications	References
BC/Chi/Alg	Molding	Physical, mechanical, Biocompatibility	Wound dressing	Chang & Chen, 2016
BC-Vaccarin	Immersion	Physical, mechanical, and biocompatibility	Wound dressing	Qiu et al., 2016
BC-xGnP	Impregnation	Thermal properties and electrical conductivity	Biosensors, tissue engineering	Kiziltas et al., 2016
BC-Fe ₂ O ₃	Immersion	Magnetic behavior	Magnetic paper, loudspeaker membranes	Barud et al., 2015
BC-HA	Immersion	Biocompatibility	Bone tissue regeneration	Duarte et al., 2015
P(3HB)-g-BC	Laccase-assisted grafting	Thermo-mechanical strength	Bio-plastics, Biomedical	Iqbal et al., 2014c
AMPS-g-BC	Ultraviolet-induced polymerization	Conductivity, effective methanol barrier	Fuel cells	Lin et al., 2013
BC-MMTs	Immersion	Antibacterial properties	Wound dressing, regeneration materials	Ul-Islam et al., 2013
BC/GO	Vacuum-assisted self-assembly	Thermal, mechanical, conducting properties	Biochemical and electrochemical devices	Feng et al., 2012
BC-PAni	Immersion	Electrical conductivity	Flexible electrodes, flexible display devices, bio-sensors etc.	Shi et al., 2012
BC-MMT	Impregnation	Physical and mechanical properties	Biomedical	Ul-Islam et al., 2012
PANI/BC	Oxidative polymerization	Thermal, mechanical, conductivity	Flexible electrodes, display, sensors	Hu et al., 2011
BC/Chi	Immersion	Physical, mechanical, Biocompatibility	Wound dressing	Kim et al., 2011
ϵ -PL/BC	Immersion	Physical, Antibacterial	Packaging	Zhu et al., 2010

materials have drawn global efforts from numerous transnational companies as well as highly skilled research groups from around the world and diverse research areas.

Conflict of interest

Authors declare no conflicting, competing and financial interests in any capacity.

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References

- Barud HS, Tercjak A, Gutierrez J, Viali WR, Nunes ES, Ribeiro SJL, Jafellici M, Nalin M, Marques RFC (2015) Biocellulose-based flexible magnetic paper. *Journal of Applied Physics* 117: 17B734.
- Bedian L, Rodríguez AMV, Vargas GH, Parra-Saldivar R, Iqbal HMN (2017) Bio-based materials with novel characteristics for tissue engineering applications—A review. *International Journal of Biological Macromolecules* 98: 837-846.
- Bilal M, Rasheed T, Iqbal HMN, Hu H, Zhang X (2017a) Macromolecular agents with antimicrobial potentialities: A drive to combat antimicrobial resistance. *International Journal of Biological Macromolecules* 103: 554-574.
- Bilal M, Rasheed T, Iqbal HMN, Hu H, Zhang X (2017c) Silver Nanoparticles: Biosynthesis and Antimicrobial Potentialities. *International Journal of Pharmacology* 13: 832-845.
- Bilal M, Rasheed T, Iqbal HMN, Li C, Hu H, Zhang X (2017b) Development of silver nanoparticles loaded chitosan-alginate constructs with biomedical potentialities. *International Journal of Biological Macromolecules* 105: 393-400.
- Chang WS, Chen HH (2016) Physical properties of bacterial cellulose composites for wound dressings. *Food Hydrocolloids* 53: 75-83.
- Chaubey KK, Singh SV, Gupta S, Singh M, Sohal JS, Kumar N, Singh MK, Bhatia AK, Dhama K (2017) *Mycobacterium avium* subspecies paratuberculosis - an important food borne pathogen of high public health significance with special reference to India: an update. *Veterinary Quarterly* 37 : 282-299.
- Cleaveland S, Laurenson MK, Taylor LH (2001) Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 356: 991-999.
- Cloete TE (2003) Resistance mechanisms of bacteria to antimicrobial compounds. *International Biodeterioration & Biodegradation* 51: 277-282.
- Cuny C, Friedrich A, Kozzytska S, Layer F, Nübel U, Ohlsen K, Witte W (2010) Emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in different animal species. *International Journal of Medical Microbiology* 300 : 109-117.
- Daszak P, Cunningham AA, Hyatt AD (2000) Emerging infectious diseases of wildlife--threats to biodiversity and human health. *Science* 287: 443.
- De Boer E, Zwartkruis-Nahuis JTM, Wit B, Huijsdens XW, De Neeling AJ, Bosch T, Heuvelink AE (2009) Prevalence of methicillin-resistant *Staphylococcus aureus* in meat. *International Journal of Food Microbiology* 134: 52-56.
- De Neeling AJ, Van den Broek MJM, Spalburg EC, van Santen-Verheul MG, Dam-Deisz WDC, Boshuizen HC, Huijsdens XW (2007) High prevalence of methicillin resistant *Staphylococcus aureus* in pigs. *Veterinary Microbiology* 122: 366-372.
- Dhama K, Chakraborty S, Tiwari R, Verma AK, Saminathan M, Amarpal, Malik YS, Nikousefat Z, Javdani M, Khan RU (2014b) A concept paper on novel technologies boosting production and safeguarding health of humans and animals. *Research Opinion in Animal and Veterinary Sciences* 4: 353-370.
- Dhama K, Tiwari R, Chakraborty S, Kumar A, Karikalan M, Singh R, Rai RB (2013) Global warming and emerging infectious diseases of animals and humans: current scenario, challenges, solutions and future perspectives – a review. *International Journal of Current Research* 5: 1942-1958.
- Dhama K, Tiwari R, Chakraborty S, Saminathan M, Kumar A, Karthik K, Wani MY, Amarpal, Singh, SV, Rahal A (2014a) Evidence based antibacterial potentials of medicinal plants and herbs countering bacterial pathogens especially in the era of emerging drug resistance: An integrated update. *International Journal of Pharmacology* 10: 1-43.
- Dobson A, Fofopoulos J (2001) Emerging infectious pathogens of wildlife. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 356: 1001-1012.
- Dorman SE, Chaisson RE (2007) From magic bullets back to the magic mountain: the rise of extensively drug-resistant tuberculosis. *Nature Medicine* 13: 295.
- Duarte EB, Bruna S, Andrade FK, Brígida AI, Borges MF, Muniz CR, Filho MMS, Morais JPS, Feitosa JPA, Rosa MF (2015) Production of hydroxyapatite-bacterial cellulose nanocomposites from agroindustrial wastes. *Cellulose* 22: 3177-3187.

- Elegir G, Kindl A, Sadocco P, Orlandi M (2008) Development of antimicrobial cellulose packaging through laccase-mediated grafting of phenolic compounds. *Enzyme and Microbial Technology* 43: 84-92.
- Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A (2005) Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. *BMC Infectious Diseases* 5: 24.
- Feng Y, Zhang X, Shen Y, Yoshino K, Feng W (2012) A mechanically strong, flexible and conductive film based on bacterial cellulose/graphene nanocomposite. *Carbohydrate Polymers* 87: 644-649.
- Fischbach MA, Walsh CT (2009) Antibiotics for emerging pathogens. *Science* 325 : 1089-1093.
- Fowler PA, Hughes JM, Elias RM (2006) Biocomposites: technology, environmental credentials and market forces. *Journal of the Science of Food and Agriculture* 86: 1781-1789.
- Gallegos AMA, Carrera SH, Parra R, Keshavarz T, Iqbal HMN (2016) Bacterial Cellulose: A Sustainable Source to Develop Value-Added Products—A Review. *BioResources* 11: 5641-5655.
- Guan D, Hoover DG (2005) Emerging decontamination techniques for meat. Improving the safety of fresh meat 388-417.
- Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Piddock LJ (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet* 387: 176-187.
- Hu W, Chen S, Yang Z, Liu L, Wang H (2011) Flexible electrically conductive nanocomposite membrane based on bacterial cellulose and polyaniline. *The Journal of physical chemistry B* 115 : 8453-8457.
- Huijsdens XW, Van Dijk, BJ, Spalburg E, van Santen-Verheul MG, Heck ME, Pluister GN, De Neeling AJ (2006) Community-acquired MRSA and pig-farming. *Annals of Clinical Microbiology and Antimicrobials* 5 : 26.
- Iqbal HMN (2015) Development of bio-composites with novel characteristics through enzymatic grafting. PhD thesis submitted to the University of Westminster, London.
- Iqbal HMN, Dhama K, Munjal A, Khandia R, Karthik K, Dadar M, Sachan S, Latheef SK, Joshi SK (2016c) Tissue Engineering and Regenerative Medicine Potentialities of Materials-Based Novel Constructs - A Review. *Current Regenerative Medicine* 6: 29-40.
- Iqbal HMN, Kyazze G, Keshavarz T (2013) Advances in the valorization of lignocellulosic materials by biotechnology: an overview. *BioResources* 8: 3157-3176.
- Iqbal HMN, Kyazze G, Locke IC, Tron T, Keshavarz T (2015a) In situ development of self-defensive antibacterial biomaterials: phenol-g-keratin-EC based bio-composites with characteristics for biomedical applications. *Green Chemistry* 17 : 3858-3869.
- Iqbal HMN, Kyazze G, Locke IC, Tron T, Keshavarz T (2015b) Development of novel antibacterial active, HaCaT biocompatible and biodegradable CA-g-P(3HB)-EC biocomposites with caffeic acid as a functional entity. *Express Polymer Letters* 9: 764-772.
- Iqbal HMN, Kyazze G, Locke IC, Tron T, Keshavarz T (2015c) Development of bio-composites with novel characteristics: Evaluation of phenol-induced antibacterial, biocompatible and biodegradable behaviours. *Carbohydrate Polymers* 131: 197-207.
- Iqbal HMN, Kyazze G, Locke IC, Tron T, Keshavarz T (2015e) Poly (3-hydroxybutyrate)-ethyl cellulose based bio-composites with novel characteristics for infection free wound healing application. *International Journal of Biological Macromolecules* 81: 552-559.
- Iqbal HMN, Kyazze G, Tron T, Keshavarz T (2014a) “One-pot” synthesis and characterisation of novel P (3HB)–ethyl cellulose based graft composites through lipase catalysed esterification. *Polymer Chemistry* 5 : 7004-7012.
- Iqbal HMN, Kyazze G, Tron T, Keshavarz T (2014b) A preliminary study on the development and characterisation of enzymatically grafted P (3HB)-ethyl cellulose based novel composites. *Cellulose* 21: 3613-3621.
- Iqbal HMN, Kyazze G, Tron T, Keshavarz T (2015d) Laccase-assisted approach to graft multifunctional materials of interest: Keratin-EC based novel composites and their characterisation. *Macromolecular Materials and Engineering* 300: 712-720.
- Iqbal HMN, Kyazze G, Tron T, Keshavarz T (2016a) Laccase from *Aspergillus niger*: A novel tool to graft multifunctional materials of interests and their characterization. *Saudi Journal of Biological Sciences In-Press*, DOI: 10.1016/j.sjbs.2016.01.027.
- Iqbal HMN, Kyazze G, Tron T, Keshavarz T (2014c) Laccase-assisted grafting of poly (3-hydroxybutyrate) onto the bacterial cellulose as backbone polymer: Development and characterisation. *Carbohydrate Polymers* 113: 131-137.
- Iqbal HMN, Dhama K, Munjal A, Khandia R, Karthik K, Dadar M, Sachan S, Latheef SK, Joshi SK (2016b) Tissue Engineering and Regenerative Medicine Potentialities of Materials - Based Novel Constructs - A Review. *Recent Patents on Inflammation & Allergy Drug Discovery* 10: 86-93.

- Jindal AK, Pandya K, Khan ID (2015) Antimicrobial resistance: A public health challenge. *Medical Journal Armed Forces India* 71: 178-181.
- Kennedy AD, Otto M, Braughton KR, Whitney AR, Chen L, Mathema B, Kreiswirth BN (2008) Epidemic community-associated methicillin-resistant *Staphylococcus aureus*: recent clonal expansion and diversification. *Proceedings of the National Academy of Sciences* 105: 1327-1332.
- Khanna T, Friendship R, Dewey C, Weese JS (2008) Methicillin resistant *Staphylococcus aureus* colonization in pigs and pig farmers. *Veterinary Microbiology* 128: 298-303.
- Khosa MA, Ullah A (2013) A sustainable role of keratin biopolymer in green chemistry: a review. *J Food Processing & Beverages* 1: 8.
- Kim J, Cai Z, Lee HS, Choi GS, Lee DH, Jo C (2011) Preparation and characterization of a bacterial cellulose/chitosan composite for potential biomedical application. *Journal of Polymer Research* 18: 739-744.
- Kiziltas EE, Kiziltas A, Rhodes K, Emanetoglu NW, Blumentritt M, Gardner DJ (2016) Electrically conductive nano graphite-filled bacterial cellulose composites. *Carbohydrate Polymers* 136: 1144-1151.
- Lee JH (2006) Occurrence of methicillin-resistant *Staphylococcus aureus* strains from cattle and chicken, and analyses of their *mecA*, *mecR1* and *mecI* genes. *Veterinary Microbiology* 114: 155-159.
- Lin CW, Liang SS, Chen SW, Lai JT (2013) Sorption and transport properties of 2-acrylamido-2-methyl-1-propanesulfonic acid-grafted bacterial cellulose membranes for fuel cell application. *Journal of Power Sources* 232: 297-305.
- Lu Z, Zhang X, Li Z, Wu Z, Song J, Li C (2015) Composite copolymer hybrid silver nanoparticles: preparation and characterization of antibacterial activity and cytotoxicity. *Polymer Chemistry* 6: 772-779.
- Michl TD, Locock KE, Stevens NE, Hayball JD, Vasilev K, Postma A, Griesser HJ (2014) RAFT-derived antimicrobial polymethacrylates: elucidating the impact of end-groups on activity and cytotoxicity. *Polymer Chemistry* 5: 5813-5822.
- Milovanovic S, Stamenic M, Markovic D, Radetic M, Zizovic I (2013) Solubility of thymol in supercritical carbon dioxide and its impregnation on cotton gauze. *The Journal of Supercritical Fluids* 84: 173-181.
- Nair LS, Laurencin CT (2007) Biodegradable polymers as biomaterials. *Progress in Polymer Science* 32: 762-798.
- Nesbakken T (1992) Epidemiological and food hygienic aspects of *Yersinia enterocolitica* with special reference to the pig as a suspected source of infection. Thesis. Norwegian College of Veterinary Medicine, Oslo.
- Plackett D, Andersen TL, Pedersen WB, Nielsen L (2003) Biodegradable composites based on L-poly lactide and jute fibres. *Composites Science and Technology* 63: 1287-1296.
- Prasad M, Lambe UP, Brar B, Shah I, Manimegalai J, Ranjan K, Rao R, Kumar S, Mahant S, Khurana SK, Iqbal HMN, Dhama, K, Misri J, Prasad G (2018) Nanotherapeutics: An insight into healthcare and multi-dimensional applications in medical sector of the modern world. *Biomedicine & Pharmacotherapy* 97: 1521-1537
- Pu S, Han F, Ge B (2009) Isolation and characterization of methicillin-resistant *Staphylococcus aureus* strains from Louisiana retail meats. *Applied and Environmental Microbiology* 75: 265-267.
- Ramees TP, Dhama K, Karthik K, Rathore RS, Kumar A, Saminathan M, Tiwari R, Malik YS, Singh RK (2017) *Arcobacter*: an emerging food-borne zoonotic pathogen, its public health concerns and advances in diagnosis and control - a comprehensive review. *Veterinary Quarterly* 37:136-161.
- Qiu Y, Qiu L, Cui J, Wei Q (2016) Bacterial cellulose and bacterial cellulose-vaccarin membranes for wound healing. *Materials Science and Engineering: C* 59: 303-309.
- Rasheed T, Bilal M, Iqbal HMN, Li C (2017) Green biosynthesis of silver nanoparticles using leaves extract of *Artemisia vulgaris* and their potential biomedical applications. *Colloids and Surfaces B: Biointerfaces* 158: 408-415.
- Rukmani A, Sundrarajan M (2012) Inclusion of antibacterial agent thymol on β -cyclodextrin-grafted organic cotton. *Journal of Industrial Textiles* 42: 132-144.
- Shahidi S, Aslan N, Ghoranneviss M, Korachi M (2014) Effect of thymol on the antibacterial efficiency of plasma-treated cotton fabric. *Cellulose* 21: 1933-1943.
- Shi Z, Zang S, Jiang F, Huang L, Lu D, Ma Y, Yang G (2012) In situ nano-assembly of bacterial cellulose-polyaniline composites. *RSC Advances* 2: 1040-1046.
- Singh RK, Dhama K, Malik YS, Ramakrishnan MA, Karthik K, Tiwari R, Saurabh S, Sachan S, Joshi SK (2016) Zika virus – emergence, evolution, pathology, diagnosis, and control: current global scenario and future perspectives – a comprehensive review. *The Veterinary Quarterly* 36:150-175. doi: 10.1080/01652176.2016.1188333.

- Singh RK, Dhama K, Malik YS, Ramakrishnan MA, Karthik K, Tiwari R, Munjal A, Saminathan M, Sachan S, Desingu PA, Kattoor JJ, Iqbal HM, Joshi SK (2017) Ebola virus – epidemiology, diagnosis and control: threat to humans, lessons learnt and preparedness plans - An update on its 40 year’s journey. *The Veterinary Quarterly* 37: 98-135.
- Skovgaard N (2007) New trends in emerging pathogens. *International Journal of Food Microbiology* 120: 217-224.
- Smith TC, Pearson N (2011) The emergence of *Staphylococcus aureus* ST398. *Vector-Borne and Zoonotic Diseases* 11: 327-339.
- Tenover FC, McDougal LK, Goering RV, Killgore G, Projan SJ, Patel JB, Dunman PM (2006) Characterization of a strain of community-associated methicillin-resistant *Staphylococcus aureus* widely disseminated in the United States. *Journal of Clinical Microbiology* 44: 108-118.
- Tiwari R, Chakraborty S, Dhama, K, Rajagunalan S, Singh, SV (2013) Antibiotic resistance - an emerging health problem: causes, worries, challenges and solutions – a review. *International Journal of Current Research* 5: 1880-1892.
- Tiwari R, Latheef SK, Ahmed I, Iqbal HMN, Bule MH, Dhama K, Samad HA, Karthik K, Alagawany M, El-Hack MEA, Yatoo MI, Farag MR (2018) Herbal immunomodulators, a remedial panacea for the designing and developing effective drugs and medicines: Current scenario and future prospects. *Current Drug Metabolism* 2018 Jan 29. doi: 10.2174/1389200219666180129125436. [Epub ahead of print]
- Tristan A, Bes M, Meugnier H, Lina G, Bozdogan B, Courvalin P, Etienne J (2007) Global distribution of Panton-Valentine leukocidin-positive methicillin-resistant *Staphylococcus aureus*, 2006. *Emerging Infectious Diseases* 13: 594.
- UK Five Year Antimicrobial Resistance Strategy 2013 to 2018 (PDF). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf accessed on November 16, 2017.
- Ul-Islam M, Khan T, Khattak WA, Park JK (2013) Bacterial cellulose-MMTs nanoreinforced composite films: novel wound dressing material with antibacterial properties. *Cellulose* 20: 589-596.
- Ul-Islam M, Khan T, Park JK (2012) Nanoreinforced bacterial cellulose-montmorillonite composites for biomedical applications. *Carbohydrate Polymers* 89: 1189-1197.
- Ultee A, Bennik MHJ, Moezelaar R (2002) The phenolic hydroxyl group of carvacrol is essential for action against the food-borne pathogen *Bacillus cereus*. *Applied and Environmental Microbiology* 68: 1561-1568.
- Van Loo I, Huijsdens X, Tiemersma E, De Neeling A, van de Sande-Bruinsma N, Beaujean D, Kluytmans J (2007) Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. *Emerging Infectious Diseases* 13: 1834.
- Veras HN, Rodrigues FF, Colares AV, Menezes IR, Coutinho HD, Botelho MA, Costa JG (2012) Synergistic antibiotic activity of volatile compounds from the essential oil of *Lippia sidoides* and thymol. *Fitoterapia* 83: 508-512.
- Wang L, He S, Wu X, Liang S, Mu Z, Wei J, Wei S (2014) Polyetheretherketone/nano-fluorohydroxyapatite composite with antimicrobial activity and osseointegration properties. *Biomaterials* 35: 6758-6775.
- Waters AE, Contente-Cuomo T, Buchhagen J, Liu CM, Watson L, Pearce K, Keim PS (2011) Multidrug-resistant *Staphylococcus aureus* in US meat and poultry. *Clinical Infectious Diseases* 52: 1227-1230.
- Witte W, Strommenger B, Cuny C, Heuck D, Nuebel U (2007) Methicillin-resistant *Staphylococcus aureus* containing the Panton-Valentine leukocidin gene in Germany in 2005 and 2006. *Journal of Antimicrobial Chemotherapy* 60: 1258-1263.
- Woolhouse ME (2002) Population biology of emerging and re-emerging pathogens. *Trends in Microbiology* 10: s3-s7.
- Woolhouse MEJ, Dye C (2001) Population biology of emerging and re-emerging pathogens. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* B 356L 981-1106.
- Zaheer Z, Rahman S, Zaherre I, Abbas G, Younas T (2017) Methicillin-resistant *Staphylococcus aureus* in poultry-an emerging concern related to future epidemic. *Matrix Science Medica (MSM)* 1: 15-18.
- Zhu H, Jia S, Yang H, Tang W, Jia Y, Tan Z (2010) Characterization of bacteriostatic sausage casing: A composite of bacterial cellulose embedded with ϵ -polylysine. *Food Science and Biotechnology* 19: 1479-1484.