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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); Johne's disease (*Mycobacterium avium* subsp. *paratuberculosis*) (Chaubey 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 cased 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

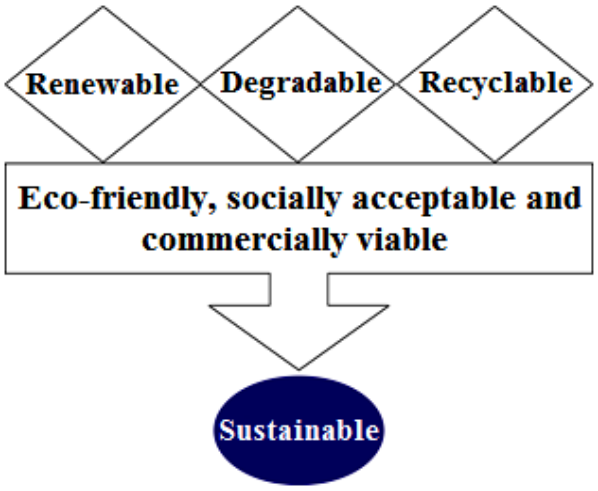

Figure 1 Concept of "sustainability" (Reproduced with permission from Iqbal, 2015; Gallegos et al., 2016).

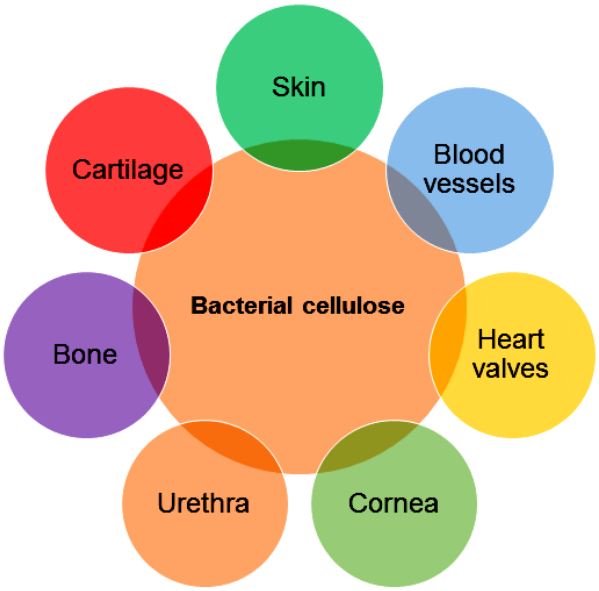

Figure 2 Prospects for the various biomedical applications of BC and BC-based materials (Reproduced with permission from Gallegos et al., 2016).

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 (Khosa & 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. I*n 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).

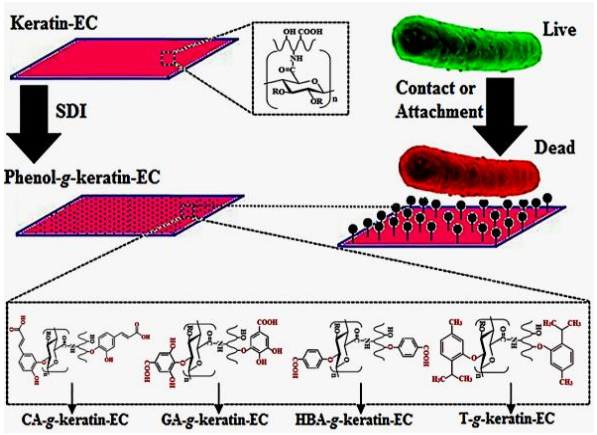

Figure 3 The design and antibacterial behavior of phenol-g-keratin-EC based materials (Reproduced from Iqbal et al., 2015a, with permission from The Royal Society of Chemistry).

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

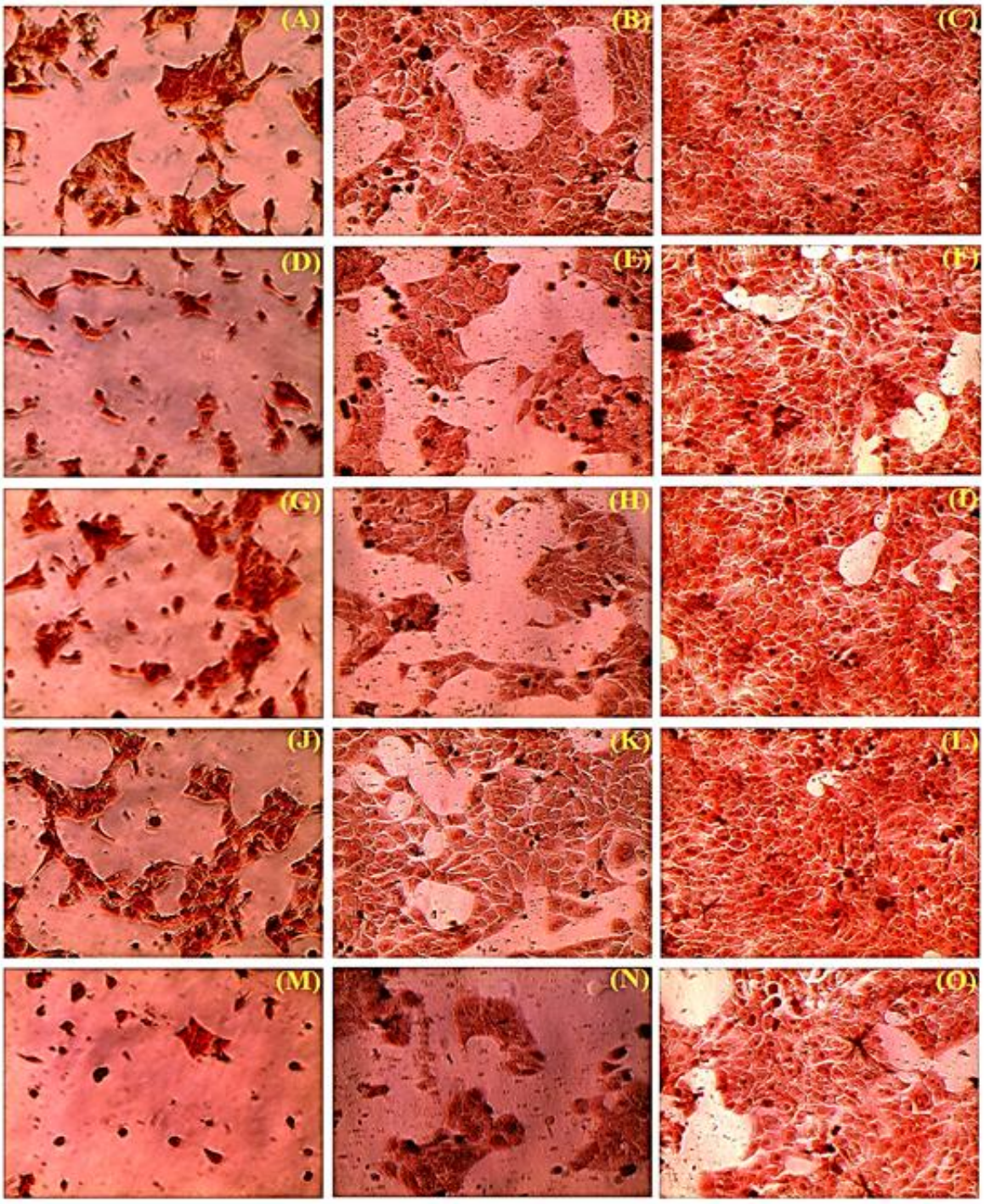

Figure 4 Adherent morphology of stained images of human keratinocytes-like HaCaT cells seeded onto the composite surfaces. Images A, B, and C represent the HaCaT cells on native P(3HB)-EC composite (i.e., 0CA-*g*-P(3HB)-EC) after 1, 3 and 5 days of incubation, respectively; images D, E, and F represent 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).

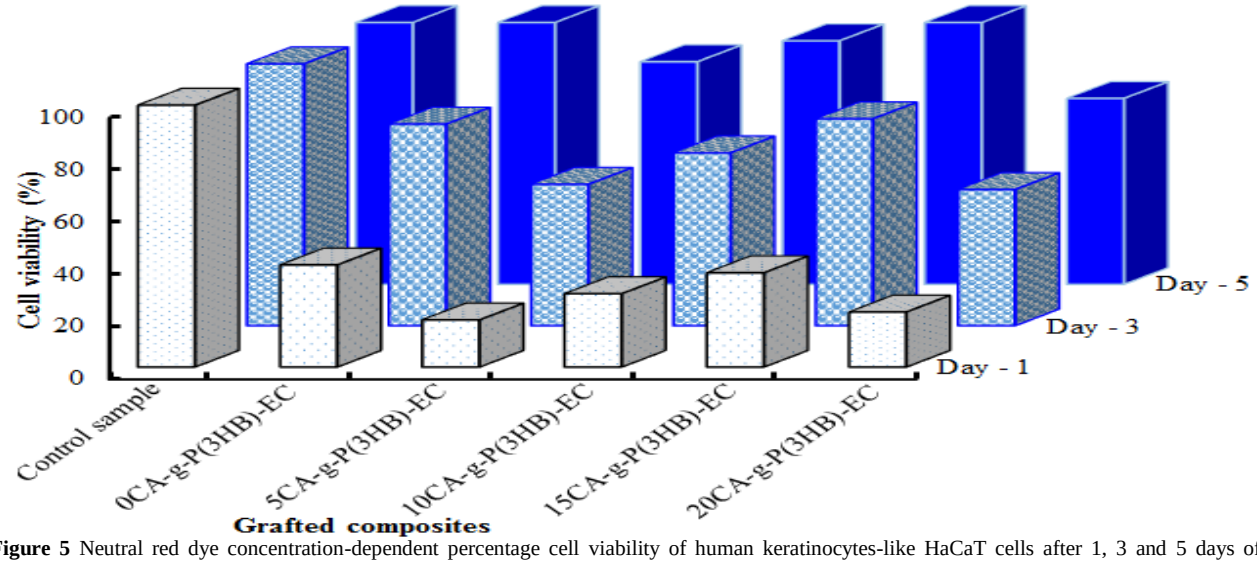

Figure 5 Neutral red dye concentration-dependent percentage cell viability of human keratinocytes-like HaCaT cells after 1, 3 and 5 days of incubation onto the CA-*g*-P(3HB)-EC composite surfaces (mean ± SD, n = 3) (Reproduced with permission from Iqbal, 2015; Iqbal et al., 2015e).

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_2O_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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