Exosomes: the natural bio-nanomedicine

Review Article

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ABSTRACT

Nanoparticles are naturally present or engineered particles. They are characterized by their tiny sizes (less than 100 nanometers) with high surface area to volume ratio. This exclusive minute size gives them many properties that allow them to be broadly used in different industries like cosmetics, beverages, and food packing. Additionally, they have the capabilities to enter the mammalian body through ingestion, inhalation, or cutaneous absorption. Besides, they can modify the pharmacokinetics and pharmacodynamics of the drugs affecting their distribution throughout body tissues. Amongst the nanoparticles, gold nanoparticles (Au-NPs) are widely used in pacemakers, stents, implants and delivery in medicine, pharmacy, and industry. As well, they are encouragingly used as a vehicle for chemotherapy. In addition, they can be used to recognize and control certain microorganisms' growth and to prepare vaccines for certain diseases. Exosomes are the mini versions of the cells from which they are released by exocytosis. They can selectively home to different cells and tissues through different mechanisms introducing their cargoes inside these target cells modifying their behavior and fate. They can be isolated from different cells like stem cells by different mechanisms. This work was aiming at identifying the advantages and disadvantages of exosomes as a natural bio-nanomedicine, especially those extracted from stem cells.

Key Words: Exosomes, nano-medicine, nanoparticles, stem cell-exosomes.

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Exosomes are one of the extracellular vesicles. These vesicles are classified based on their cellular origin and/or biological function, into[1]:

Exosomes Figure 1A[2], micro-vesicles Figure 1B[3] which are extracellular budding of different shapes and sizes and apoptotic bodies Figure 1C[3] which are different sized cytoplasmic fragments containing parts of the nucleus occurred at the end stage of the programmed cell death, apoptosis.

Exosome contents and release:

Exosomes are formed via the process of endosomal pathway as reported by[3]. The process is recorded in Figure 2A[4] to start by cell membrane invagination incorporating certain surface proteins through the process of endocytosis to form early endosomes. Then, there is internalization of certain cytoplasmic contents, such as mitochondria, inside the early endosomes changing them to late endosomes. Such late endosomes enlarge forming large multi-vesicular bodies (MVBs). Multiple membrane invaginations of these MVBs result in formation of multiple intraluminal vesicles (ILVs) Figure 2B[3]. These ILVs have two fates according to what was documented previously by[5] Figure 2C. They stated that ILVs either remain inside the cells as exosomes that pass to the cell membrane, fuse with it, then released to the extracellular compartment via the process of exocytosis or fuse with lysosomes producing autolysosomes.

Exosomes power of escaping the extracellular clearance and specific tissue homing:

Exosomes can be released by all eukaryotic cells. So, they are recently considered as mini versions of their parent cells[6] where they are nano-vesicles (30 - 100 nm) carrying different cellular molecules. They are regarded as complex cargoes of protein such as heat shoch proteins (HSPs) [HSP90, HSP70 and HSP60], cytoskeleton proteins [actin, tubulin, profilin, myosin and tropomyosin], signaling proteins [mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase 1 / 2 (ERK1 / 2), catenin, G-protein and syntenin] and enzymes [Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), enolase, aldolase,

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pyruvate kinase, ATPase and Phosphoglycerate kinase 1 (PGK1)]. Additionally, they transport lipids as profillins, cholesterols, sphingolipids and ceramids and nucleic acids as mRNA, miRNA, long non-coding RNAs (LncRNA), tRNA and DNA. They also have tetraspanins as CD63, CD81 and CD9, adhesion molecules as Milk fat globule-EGF factor 8 protein (MFGE8), Intercellular Adhesion Molecule 1 (ICAM-1) and CD58 besides molecules for membrane transport and fusion like Lysosomal-associated membrane protein 1 and 2 (LAMP1, LAMP2) and CD13[7].

The specific sorting of these bioactive substances is ensured by two mechanisms; either Endosomal sorting complex required for transport (ESCRT)-dependent mechanism or ESCRT-independent mechanism (involved tetraspanins and lipids). The exosomes are released by fusion of MVBs to the cell membrane helped by soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) protein and cytoskeleton proteins, especially actin[8].

Exosomes power of escaping the extracellular clearance and specific tissue homing:

In the extracellular fluid, exosomes are able to escape clearance by the complement, mononuclear phagocytic system and immune system due to the presence of certain molecules such as the death receptor/ligand complex (Fas/FasL) that induces apoptosis of helper T-cells, CD59 that prevents membrane attack complex (MAC) formation by complements, CD47 that prevents phagocytosis and CD55 that prevents binding of complement C3b[9].

Homing of exosomes was reported by[10] through cell-specific manner to target cells. This is followed by unloading for their cargo[11] achieved via different processes; receptor-ligand interaction, fusion, or endocytosis[12]. Once internalized, they fuse with the endosomes, resulting in the horizontal transfer of their content to the target cells' cytoplasm[6].

Exosomes versus nanoparticles in nanomedicine:

A former work[13] reported that numerous research targeted exosomes as a promising natural "bio-nanomedicine" and recorded their advantages over synthetic nanomedicine. Such approach was based on that they are natural so, they provide natural biocompatibility, higher stability, and longer distance of intercellular communication. In addition, they penetrate tight tissue structures, such as the blood brain barrier and can selectively fuse cells and target specific tissues.

Moreover, they are safer than the synthetic nanoparticles [e.g. gold nanoparticles (AU-NPs)] which were proved to have oxidative, inflammatory, degenerative, and apoptotic effects on rats' lungs[14], rats' liver[15] and mice brain[16]. In addition to our previous work[17] that studied the effects of daily oral administration of Au-NPs for two weeks on the pituitary pars distalis in adult male albino rats. They detected the presence of Au-NPs in pars distalis following their administration using inductively coupled plasma (ICP)-mass spectrometry. This was accompanied by a significant decrease in the serum levels of LH, FSH and prolactin (PRL) and in the pituitary homogenate level of Bcl-2 (anti-apoptotic marker) in Au-NPs group versus the control group. However, the pituitary homogenate levels of tumor necrosis factor- α (TNF-α) and malondialdehyde (MDA) (peroxidation marker) were significantly increased in Au-NPs group compared to the control group.

The authors also reported pars distalis disorganization, inflammatory reaction, and cellular degenerative changes Figures 3A and 3E. Such findings were confirmed by the significant increase in the mean area percent of Cytochrome-C (marker for apoptosis) in the Au-NPs group versus the control group Figures 3F and 3H.

Methods of exosome isolation and identification:

Exosomes have different methods to be isolated according to[7]:

- Ultra-centrifugation.

- Ultra-filtration.

- Immuno-affinity chromatography.

- Size exclusion chromatography.

Previous research[6] stated that from these methods, the most accepted and widely used one for purifying exosomes from culture media is serial centrifugation (to remove cells and microvesicles) followed by exosomes concentration via ultra-centrifugation and subsequent density gradient purification[18].

Typically, exosomes are identified after their isolation by their sizes ranging from 30100- nm (average 50 nm). In addition to their morphology which is cup-shaped, spheroid by electron microscope Figures 4A and 4B[19, 20]. Moreover, they have specific surface marker proteins such as tetraspanins [CD9, CD63 and CD81] Figure 4C[19].

Uses of exosomes in nanomedicine:

Exosomes can be used in diagnosis and prognosis or in therapy and drug delivery[13].

1) Exosomes as biomarkers for diagnosis of various diseases:

Exosomes can be used as biomarkers for diagnosis and prognosis of different diseases such as serum exosomes in hepatocellular carcinoma[21], salivary exosomes in pancreato-biliary tract cancer[22] and urinary exosomes in kidney injury[23].

This is applicable as exosomes are considered as "fingerprints" of the donor cells[24]. In addition, they are found in almost all body fluids such as blood, urine, breast milk, CSF, semen, amniotic fluid and ascitic fluid[6]. So, they can be isolated easily from patients in a non-invasive manner[25].

2) Exosomes as therapeutic tool:

They can be used in therapy of different diseases like CVS, respiratory and neurodegenerative ones[26]. This is because they are physicochemical stable biological nanoparticles[11]. They specifically target cells or tissues[6]. In addition, they can avoid the issue of immunogenicity, so, the incorporated therapeutic agents can be delivered without the rapid clearance or toxicity[27]. Besides, they can cross different biological barriers[28].

In therapy, exosomes can be used as nano-drug carriers or as nanomedicine by themselves.

Exosomes as nano-drug carrier:

They can be loaded by the drugs either passively or actively[26]:

In the passive loading, the drug is either incubated with the donor cell then exosomes are isolated, or the exosomes are isolated first then incubated with the drug. While in active loading, the exosomes are actively loaded by the drug using different methods such as transfection reagent, electroporation, incubation, sonication, freezing/thawing cycle, incubation with membrane permeabilizer or extrusion.

Exosomes as nanomedicine:

They can be isolated from genetically modified cells where the desired nucleic acids are loaded into the donor cells via vector transfection-based strategy. The donor cells generate RNAs/proteins and pack them into exosomes.

Moreover, they can be derived from stem cells after being cultured, isolated, and identified[29]. Notably, exosomes can be isolated from different types of stem cells: ordinary stem cells, loaded stem cells or pre-conditioned stem cells.

Ordinary stem cell-exosomes:

Exosomes derived from ordinary stem cells were used in previous research for management of different diseases in different organs such as liver, kidneys, cardio-vascular system (CVS) and nervous system[30].

Moreover, they were used in our former research that studied the potential therapeutic effects of single intravenous dose of exosomes derived from adipose mesenchymal stem cells on a male rat model of acetic acid-induced ulcerative colitis[31]. It reported identification of ordinary stem cells-exosomes by TEM Figure 5[1], homing of these exosomes in the colon mucosa at day 3, 9 and 16 of the experiment Figure 5[2 - 4]. On day 9, these exosomes were proved to partially restore the histological picture of the colonic mucosa and ameliorate the acetic acid-induced inflammatory and degenerative effects. On day 16, almost normal histological architecture of the colonic mucosa was achieved in the exosomes treated group Figure 5A - J.

Loaded stem cell-exosomes:

Stem cells can be loaded with different drugs as antioxidants[32] or anti-cancerous[33, 28] either actively or passively as mentioned before, then the drug will be incorporated within the stem cell-exosomes[34].

Preconditioned (stimulated, stressed, or genetically modified) stem cell-exosomes:

As exosome characteristics vary depending on the status of the SCs from which they are derived, and the SC status changes in response to external stimuli[7], Pre-conditioning of SCs[7] with cytokines, hypoxia, and chemicals improve their immunosuppressive, immunomodulatory, and regenerative effects[35]. Moreover, gene and cell surface modification of MSCs enhance their therapeutic efficacy[36]. So, SCs Pre-conditioning could increase exosome activity via increasing MSCs function[37].

Preconditioned stem cell-exosomes were used in much research to treat, liver diseases[38] and CVS

diseases[37]. In addition, heat shock preconditioned stem cell-exosomes were used in our former study[39]. Such work studied and compared the effect of single IV dose of non-heat shock bone marrow mesenchymal stem cells-exosomes (non-HSBMMSCs) and heat shock bone marrow mesenchymal stem cells-exosomes (HSBMMSCs) on experimentally induced myocardial infarction (MI) in its acute stage (3 days) and chronic stage (28 days).

It stated homing of both non-HSBMMSCs and HSBMMSCs in the myocardium one day following their administration in myocardium of the MI subgroups and their absence in the control group Figure 6[1 - 4]. Moreover, there were cardiac degenerative changes in MI group deteriorating from day 3 (acute stage) towards day 28 (chronic stage). These changes were improved with administration of non-HSBMMSCs and showed marked improvement with HSBMMSCs treatment Figure 6A - G.

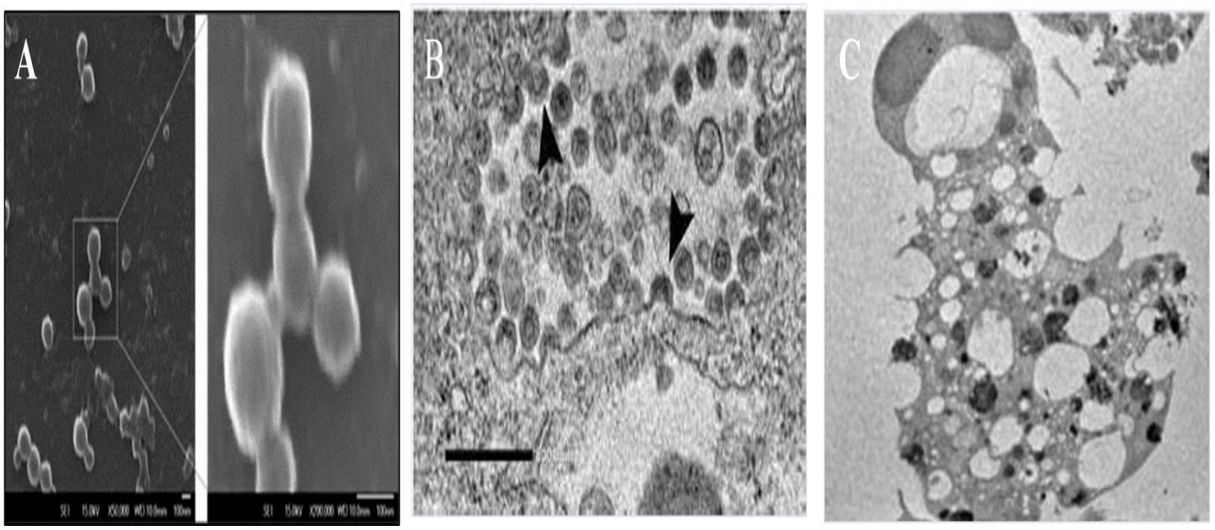

Figure 1: A: SEM image: exosomes [Scale bar 100 nm] (2). B: TEM image for micro-vesicles liberation (arrowheads). C: TEM image for an apoptotic cell (3).

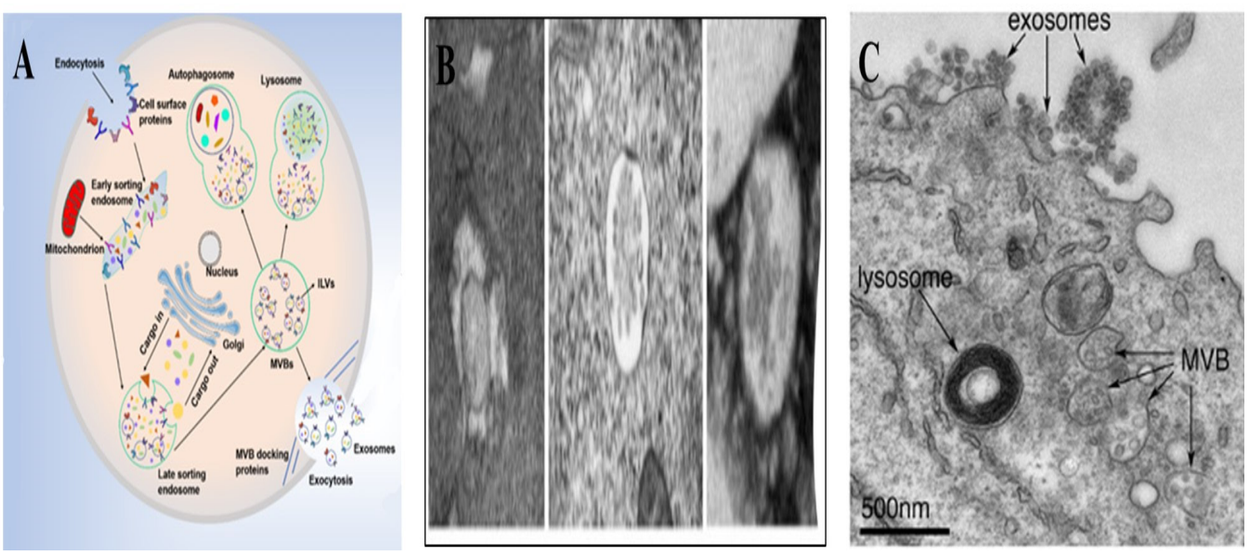

Figure 2: A: Exosomes biogenesis (4). B: TEM images: MVB invaginations, MVB enclosing a lot of exosomes, MVB fuses with the cell membrane (3). C: TEM image: newly expelled exosomes at the plasma membrane, MVB and lysosomes (5).

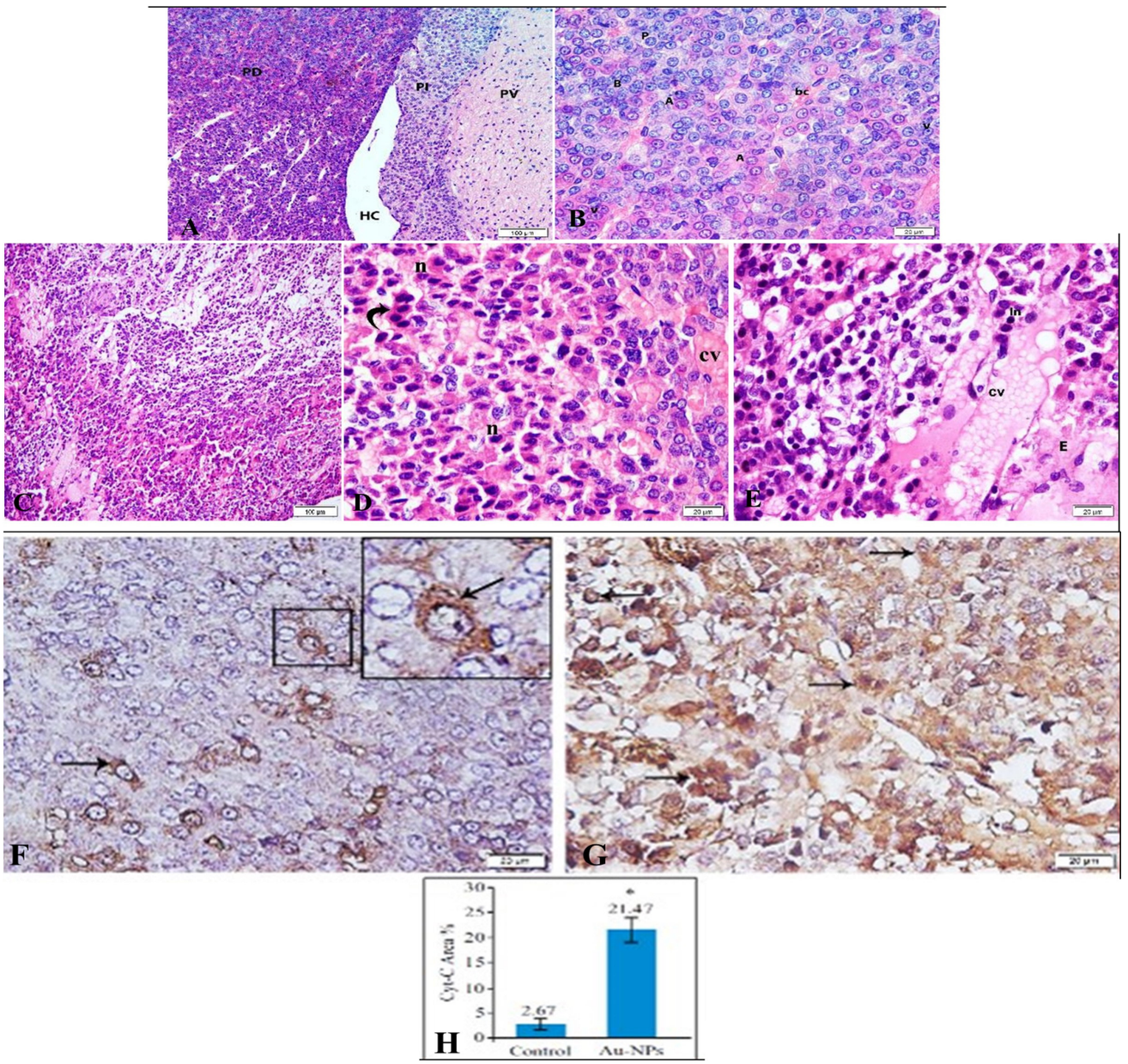

Figure 3: Photomicrographs of H and E-stained pituitary sections. The pituitary glands in the control group (A and B) were presented in (A) with the normal tissue architecture demonstrating pars distalis (PD) on the left, the hypophyseal cleft (HC) in the middle and pars intermedia (PI) and pars nervosa (PV) on the right. In (B) the pars distalis shows blood capillaries (BC) between cellular cords of chromophobes (P), acidophils (A) and basophils (B). All the cell types reveal rounded vesicular nuclei (v). The pituitary of rats in the Au-NP group (C, D, E) demonstrates disturbed architecture in (C). In (D) there are visible shrunken cells with deeply eosinophilic cytoplasm (curved arrow) as well as cells with shrunken nuclei (n). In (E) inflammatory cell infiltration (In) and dilated congested vein (cv) with extra-vascular exudation (E) are noticed. Magnifications: (A, C) 100×; (B, D, E) 400×. Photomicrographs of immunohistochemistry in the pars distalis sections for Cyt-C: The control group (F) shows few cells with positive cytoplasmic immunoreaction (arrow). The upper right inset: a higher magnification of the boxed area illustrating the cytoplasmic reaction (arrow) in a hormonal cell. The Au-NP group (G) displays abundant positive immunoreaction (arrow). (H) The mean area percent of Cyt-C immunoreactivity. Data are presented as mean ± SD. *significantly different from control, $p < 0.05$. Magnifications: F, G: 400×; Inset: 1000× (17).

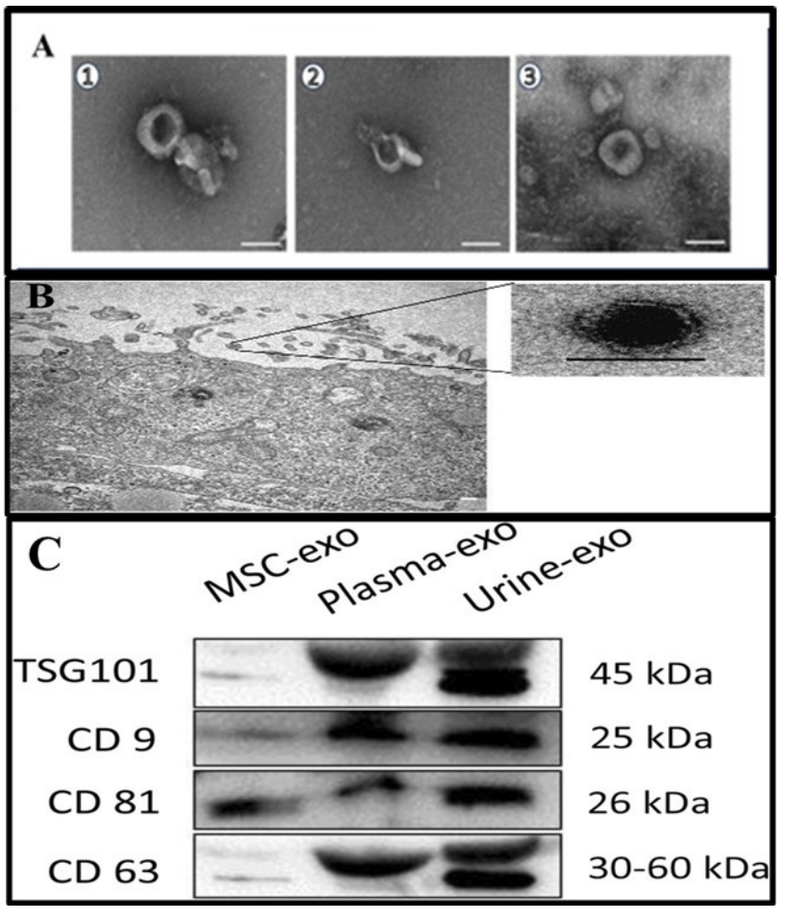

Figure 4: A: TEM of exosomes from feline samples. (1): ADMSC culture medium, (2): plasma, (3): urine. Exosomes were cup-shaped and in size from 30 to 100 nm (19). B: TEM images: Left: Electron micrographs of exosomes released from neural stem cell membrane, scale 200 nm. Right: Exosome with a lipid bilayer membrane sizing 50 nm (20). C: Western Blot analysis of exosomes from feline samples. Surface Markers TSG101, CD9, CD63 and CD81 are positively expressed in exosomes secreted from ADMSC culture medium, plasma, and urine (19).

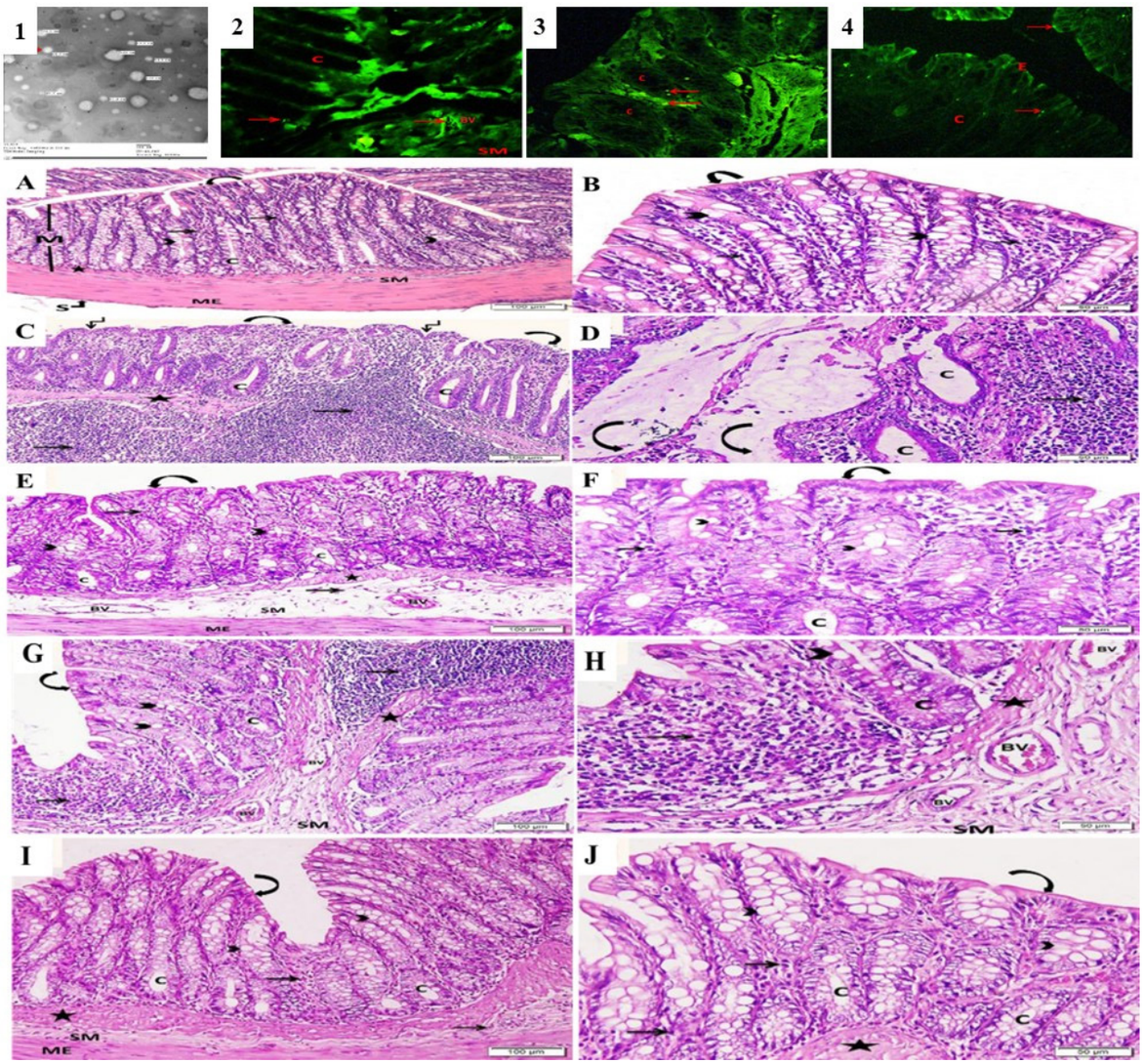

Figure 5: 1: TEM micrograph showing exosomes in ADMSCs - culture media (red arrow). Magnification: x60000. Photomicrograph of unstained colonic sections: 2: exosome-treated group at the 3rd day of the experiment showing PKH26 labeled ADMSCs-E aggregates (arrow) at the lamina propria around the crypts (C) also within the blood vessel of the submucosa (SM). 3: exosome-treated group at the 9th day of the experiment viewing numerous PKH26 labeled ADMSCs-E aggregates (arrows) at the lamina propria and inside the crypts (C). 4: exosome-treated group at the 16th day of the experiment showing some PKH26 labeled ADMSCs-E aggregates (arrows) at the lamina propria around crypts (C) and surface epithelium (E). Fluorescent microscopy, Magnifications × 200. Photomicrograph of a colonic section: A and B: control group showing normal colon with intact mucosa (M), continuous surface epithelium with intact brush border (curved arrow), numerous goblet cells (arrowhead) and regularly arranged, closely related crypts (C) resting on muscularis mucosa (star). Minimal inflammatory cells are observed in between the crypts (arrow). Note the normal appearance of the submucosa (SM), muscularis externa (ME) and the covering serosa (S). C and D: colitis group on 9th day of the experiment exhibiting newly formed crypts (C), partially intact surface epithelium (elbow arrows) with persistent areas of discontinuation (curved arrows) and edematous submucosa with extensive cellular infiltration (arrows) piercing the muscularis mucosa (star) reaching the lamina propria. E and F: exosome-treated group on day 9 showing partial restoration of cryptal (C) architecture with intact surface epithelium (curved arrow) and goblet cells (arrowheads), Few inflammatory cells (arrow) in the lamina propria and the edematous submucosa (SM) with many dilated blood vessels (BV). Normal muscularis mucosa (star) is visualized. G and H: colitis group on day 16 showing partial restoration of crypt architecture (C) with continuous surface epithelium (curved arrow) and goblet cells (arrowheads). Large inflammatory cellular aggregates (arrows) are noticed where one of them piercing the muscularis mucosa (star). Edematous submucosa (SM) with many dilated blood vessels (BV) is also noted. I and J: exosome-treated group on day 16 displaying apparently normal mucosa with regularly arranged crypts (C), intact surface epithelium with intact brush border (curved arrow) and numerous goblet cells (arrowheads). Note minimal inflammatory cells (arrows) in lamina propria and the apparently normal submucosa (SM). Normal muscularis mucosa (star) is noted. H&E: A, C, E, G, and I, x100; B, D, F, H and J, x200 (31).

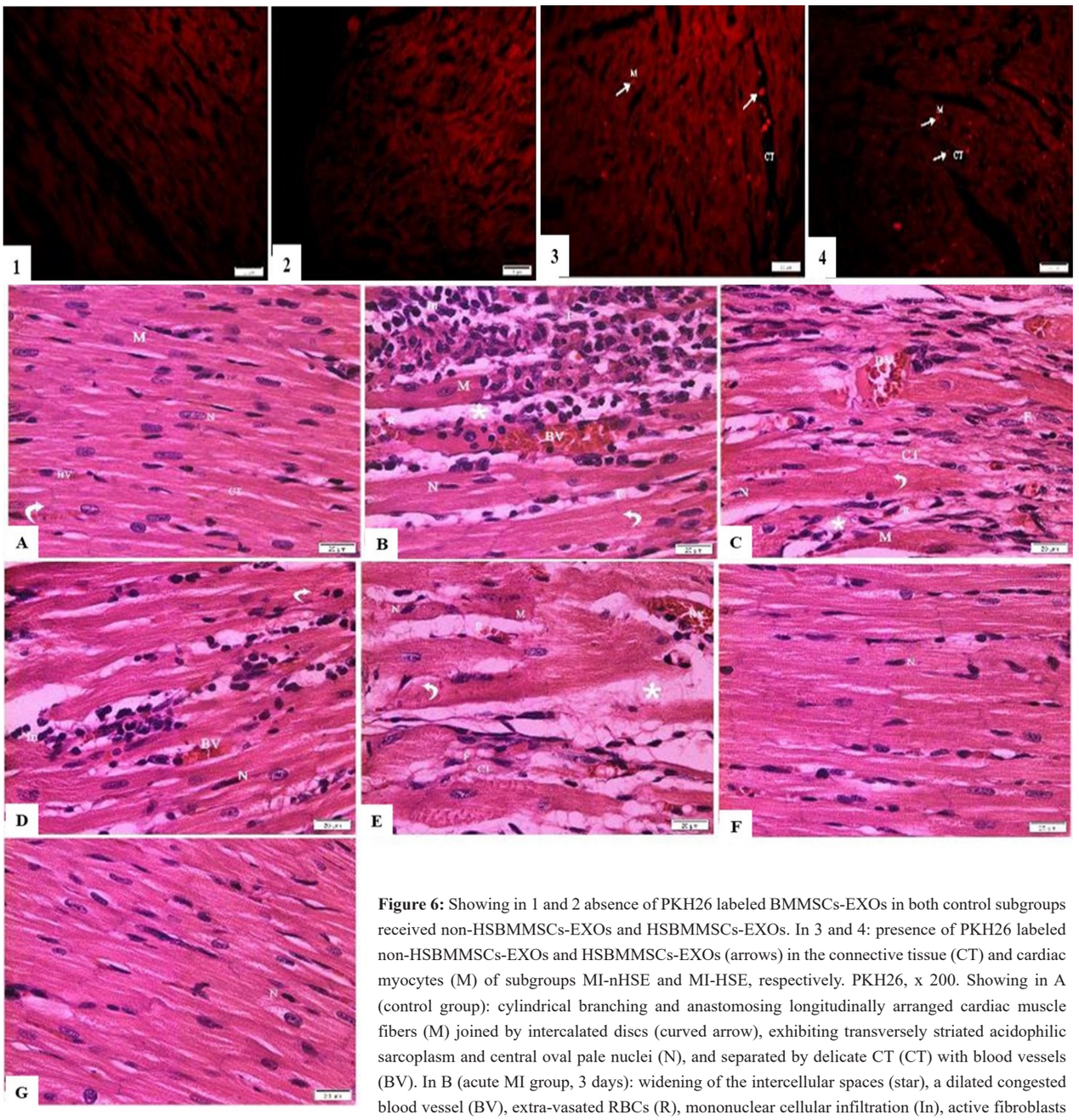

Figure 6: Showing in 1 and 2 absence of PKH26 labeled BMMSCs-EXOs in both control subgroups received non-HSBMMSCs-EXOs and HSBMMSCs-EXOs. In 3 and 4: presence of PKH26 labeled non-HSBMMSCs-EXOs and HSBMMSCs-EXOs (arrows) in the connective tissue (CT) and cardiac myocytes (M) of subgroups MI-nHSE and MI-HSE, respectively. PKH26, x 200. Showing in A (control group): cylindrical branching and anastomosing longitudinally arranged cardiac muscle fibers (M) joined by intercalated discs (curved arrow), exhibiting transversely striated acidophilic sarcoplasm and central oval pale nuclei (N), and separated by delicate CT (CT) with blood vessels (BV). In B (acute MI group, 3 days): widening of the intercellular spaces (star), a dilated congested blood vessel (BV), extra-vasated RBCs (R), mononuclear cellular infiltration (In), active fibroblasts (F), disruption of the intercalated discs (curved arrow), myocytes (M) with deeply acidophilic sarcoplasm and lost striations and others with shrunken darkly stained nuclei (N). In C (chronic MI group, 28 days): enormous widening of the intercellular spaces (star), obvious CT (CT) thickening, numerous active fibroblasts (F), blood vessels (BV) dilatation and congestion, extra-vasated RBCs (R), disrupted intercalated disc (curved arrow) and few myocytes (M) with deeply acidophilic sarcoplasm and lost striations or shrunken darkly stained nuclei (N). In D (acute MI-nHSE, 3 days): few shrunken condensed nuclei (N), intact intercalated discs (curved arrow), minimal inflammatory cell infiltration (In) and a dilated congested blood vessel (BV). In E (chronic MI-nHSE, 28 days): wide intercellular spaces (star), thickened CT (CT), active fibroblasts (F), a dilated congested blood vessel (BV), extra-vasated RBCs (R), disrupted intercalated discs (curved arrow), myocytes (M) with deeply acidophilic sarcoplasm and lost striations, shrunken darkly stained nuclei (N). In F and G (acute MI-HSE, 3 days and chronic MI-HSE, 28 days, respectively): very few shrunken darkly stained nuclei (N) in subgroups MI-HSE-3 andMI-HSE-28. H&E, x400 (39).

CONCLUSION

Exosomes are superior to other nanoparticles, so, can be used as a natural bio-nanomedicine especially those derived from stem cells as they have many advantages[7, 13]:

They carry most of the therapeutic effect of the SCs, so, they are the mediators of stem cell paracrine action and the main mechanism of disease treatment. They offer cell-free therapy, so, do not mutate, duplicate, or induce metastasis. Additionally, they avoid some cell therapy tricky problems such as cell necrosis, abnormal differentiation, or immune rejection. Moreover, their activity can be manipulated by pre-conditioning of SCs. Furthermore, they can act as carrier particles, and they can be engineered to target specific cells or tissues. Besides, they can home to the lesion tissue, which is conducive to constructing them into drug carriers.

On the other hand, they have many disadvantages[7, 40] such as: Difficult quality control where the methods of preparation, identification and purification can result in contaminated mixtures. So, the required dose is difficult to adjust. The preparation, identification and isolation methods are expensive. Additionally, stem cells have different physiological aspects, which could affect the therapeutic efficacy of the derived exosomes.

CONFLICTS OF INTEREST

There is no potential conflicts of interest among the authors.

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الملخص العربي

الإكسوسومات: الطب الحيوي الطبيعي

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الجسيمات النانوية هي جزيئات موجودة بشكل طبيعي أو مُهندسة. وتتميز بأحجامها الصغيرة (أقل من 100 نانومتر) مع نسبة مساحة سطحية عالية إلى حجم. يمنحها هذا الحجم الدقيق الحصري العديد من الخصائص التي تسمح باستخدامها على نطاق واسع في صناعات مختلفة مثل مستحضرات التجميل والمشروبات وتغليف المواد الغذائية. بالإضافة إلى ذلك، لديهم القدرة على دخول جسم الثدييات عن طريق البلع أو الاستنشاق أو الامتصاص الجلدي. علاوة على ذلك، يمكنهم تعديل الحرائك الدوائية والديناميكا الدوائية للأدوية مما يؤثر على توزيعها في جميع أنحاء أنسجة الجسم. من بين الجسيمات النانوية، تُستخدم جسيمات الذهب النانوية (Au-NPs) على نطاق واسع في أجهزة تنظيم ضربات القلب والدعامات والمزروعات والتوصيل في الطب والصيدلة والصناعة. بالإضافة إلى ذلك، يتم استخدامها بشكل مشجع كوسيلة للعلاج الكيميائي. بالإضافة إلى ذلك، يمكن استخدامها للتعرف على نمو بعض الكائنات الحية الدقيقة والتحكم فيه ولتحضير لقاحات لبعض الأمراض. الإكسوسومات هي النسخ المصغرة للخلايا التي يتم إطلاقها منها عن طريق الإخراج الخلوي. يمكنهم بشكل انتقائي أن يستوطنوا خلايا وأنسجة مختلفة من خلال آليات مختلفة لإدخال حمولاتهم داخل هذه الخلايا المستهدفة لتعديل سلوكهم ومصيرهم. ويمكن عزلها من خلايا مختلفة مثل الخلايا الجذعية بآليات مختلفة. كان هذا العمل يهدف إلى التعرف على مميزات وعيوب الإكسوسومات كدواء نانوي حيوي طبيعي، وخاصة تلك المستخرجة من الخلايا الجذعية.