

SUPPORTING INFORMATION

Table S1. List of proteins identified exclusively in *C. acnes*-derived A1 EVs under anaerobic conditions

Gene name	Accession number	Protein name	GO - Biological process	GO - Molecular function	GO - Cellular component
pyrK PPA1001 cbac_05440	WP_002517886.1	Dihydroorotate dehydrogenase B	Biosynthetic process	Binding	Membrane
cbac_03745	WP_073842171.1	PTS sugar transporter	Transport	Transferase activity	Membrane
PPA1099 cbac_05960	WP_002514993.1	PAC2 family protein	Protein processing	Unknown	Cytoplasm
pyrD cbac_05445	WP_002517834.1	Dihydroorotate dehydrogenase	Biosynthetic process	Dehydrogenase activity	Cytoplasm
PPA2168 cbac_11750	WP_002516248.1	Formimidoylglutamate deiminase	Metabolic process	Peptidase activity	Cytoplasm
cbac_02600	WP_002531152.1	Copper homeostasis protein CutC	Cellular homeostasis	Binding	Unknown
folP PPA0271 cbac_01520	WP_002517047.1	Dihydropteroate synthase	Biosynthetic process	Binding	Cytoplasm
PPA0313 cbac_01745	WP_002517195.1	NAD-dependent malic enzyme	Metabolic process	Dehydrogenase activity	Cytoplasm
hisF HMPREF0675_4424	WP_002516482.1	Imidazole glycerol phosphate synthase subunit HisF	Biosynthetic process	Lyase activity	Cytoplasm
PPA0464 cbac_02555	WP_002530084.1	Sugar phosphate isomerase/epimerase	Biosynthetic process	Isomerase activity	Membrane
PPA0464 cbac_02555	WP_002530084.1	Sugar phosphate isomerase/epimerase	Biosynthetic process	Isomerase activity	Cytoplasm
PPA1005 cbac_05460	WP_002515547.1	Fructosamine kinase	Protein processing	Kinase activity	Cytoplasm
cbac_02675	WP_002518785.1	Phosphoserine transaminase	Biosynthetic process	Transferase activity	Cytoplasm
ddl cbac_12720	WP_002515704.1	D-alanine--D-alanine ligase	Cell wall organization	Binding	Cytoplasm
thiE cbac_04840	WP_002531442.1	Thiamine-phosphate synthase	Biosynthetic process	Binding	Cytoplasm
PPA0303 cbac_01695	WP_002531197.1	Uroporphyrinogen-III synthase	Biosynthetic process	Synthase activity	Cytoplasm
HMPREF0675_4140	WP_002515011.1	Histidine triad domain protein	Transport	Catalytic activity	Membrane
cobM PPA0421 cbac_02310	WP_002515099.1	Precorrin-4 C	Biosynthetic process	Transferase activity	Unknown
hutI HMPREF0675_5232	WP_002516336.1	Imidazolonepropionate	Metabolic process	Binding	Cytoplasm
PPA1225 cbac_06630	WP_002524933.1	Pyridoxal kinase	Biosynthetic process	Kinase activity	Cytoplasm
PPA1015 cbac_05515	WP_002515534.1	Aldose epimerase	Metabolic process	Binding	Membrane
PPA1982 cbac_10760	WP_002530665.1	Phosphatase PAP2 family protein	Lipid metabolism	Phosphatase activity	Membrane
PPA0525 cbac_02915	WP_002516665.1	DNase	Degradation	Hydrolase activity	Cytoplasm
PPA1009 cbac_05480	WP_002513709.1	Possible transcriptional regulator	Transcription	Molecular function regulator	Cytoplasm
PPA1629 cbac_08845	WP_002517032.1	6-phosphogluconate dehydrogenase, decarboxylating	Metabolic process	Dehydrogenase activity	Cytoplasm
PPA2286 cbac_12435	WP_002515771.1	Phosphoglucomutase	Metabolic process	Transferase activity	Cytoplasm
PPA0106 cbac_00580	WP_002512819.1	ABC transporter substrate-binding protein	Transport	Binding	Membrane
tsaB PPA1784 cbac_09710	WP_002531267.1	Peptidase, family M22	Translation	Transferase activity	Membrane
tsaB PPA1784 cbac_09710	WP_002531267.1	Peptidase, family M22	Translation	Transferase activity	Cytoplasm
idi cbac_11445	WP_002530756.1	Isopentenyl-diphosphate Delta-isomerase	Biosynthetic process	Hydrolase activity	Cytoplasm
PPA2156 cbac_11695	WP_002530776.1	Dipeptide ABC transporter ATP-binding protein	Transport	Transporter activity	Membrane
murQ HMPREF9578_00165	WP_002513573.1	N-acetylmuramic acid 6-phosphate etherase	Metabolic process	Lyase activity	Cytoplasm
PPA2214 cbac_12030	WP_002530902.1	Electron transfer flavoprotein subunit alpha	Metabolic process	Transferase activity	Unknown
HMPREF9206_1221	WP_002512973.1	Phosphoglycerate mutase family protein	Metabolic process	Catalytic activity	Cytoplasm

menC PPA0902 cbac_04915	WP_002515608.1	o-succinylbenzoate synthase	Biosynthetic process	Synthase activity	Cytoplasm
cmk HMPREF0675_4273	WP_002516760.1	Cytidylate kinase	Metabolic process	Kinase activity	Cytoplasm
metK HMPREF0675_4255	WP_002517758.1	S-adenosylmethionine synthase	Metabolic process	Binding	Cytoplasm
cbac_03780	WP_002530937.1	Exo-alpha-sialidase	Lipid metabolism	Sialidase activity	Cytoplasm
PPA1781 cbac_09695	WP_002514786.1	8-oxo-dGTP diphosphatase	DNA repair	Hydrolase activity	Cytoplasm
PPA1544 cbac_08415	WP_002514359.1	Conserved protein	Protein processing	Binding	Cytoplasm
PPA1950 cbac_10560	WP_002523392.1	Cell division protein DedD	Metabolic process	Deaminase activity	Membrane
coaD HMPREF9578_02029	WP_002514272.1	Phosphopantetheine adenyltransferase	Biosynthetic process	Transferase activity	Cytoplasm
PPA2116 cbac_11450	WP_002530757.1	Serine protease	Biosynthetic process	Peptidase activity	Membrane
PPA0443 cbac_02415	WP_002516675.1	Cobalamin-binding protein	Transport	Binding	Cytoplasm
HMPREF0675_3579	WP_002517279.1	Transcriptional regulator, TetR family	Transcription	Molecular function regulator	Nucleoid
HMPREF0675_5283	WP_002516338.1	FAD dependent oxidoreductase	Metabolic process	Oxidoreductase activity	Cytoplasm
PPA1366 cbac_07465	WP_002516499.1	FAA hydrolase family protein	Metabolic process	Catalytic activity	Cytoplasm
manA PPA0008 cbac_00045	WP_002515893.1	Mannose-6-phosphate isomerase	Metabolic process	Isomerase activity	Cytoplasm
cbac_06585	WP_002516778.1	HAD family hydrolase	Protein processing	Hydrolase activity	Cytoplasm
PPA1377 cbac_07530	WP_002531311.1	RNA helicase	Unknown	Binding	Cytoplasm
PPA0603 cbac_03350	WP_007400924.1	Putative transcriptional regulator	Transcription	Molecular function regulator	Unknown
HMPREF0675_5327	WP_002518141.1	Transcriptional regulator, MarR family	Transcription	Molecular function regulator	Cytoplasm
gyrA PPA0010 cbac_00055	WP_002530866.1	DNA gyrase subunit A	DNA replication	Binding	Cytoplasm
cbac_02560	WP_002524726.1	Sugar phosphate isomerase/epimerase	Metabolic process	Isomerase activity	Cytoplasm
cbac_04330	WP_073885323.1	HtaA domain protein	Translation	Binding	Membrane
PPA1181 cbac_06395	WP_002516773.1	Shikimate 5-dehydrogenase	Metabolic process	Dehydrogenase activity	Cytoplasm
prcB PPA1206 cbac_06530	WP_002516776.1	20S proteasome beta-subunit	Metabolic process	Peptidase activity	Cytoplasm
PPA0947 cbac_05145	WP_002513775.1	DNA-binding response regulator	Transcription	Molecular function regulator	Cytoplasm
HMPREF0675_5322	WP_002516444.1	Putative 3-methyladenine DNA glycosylase	DNA replication	Binding	Nucleoid
HMPREF0675_5322	WP_002516444.1	Putative 3-methyladenine DNA glycosylase	DNA replication	Binding	Cytoplasm
PPA1371 cbac_07495	WP_002516506.1	Putative transferase	Biosynthetic process	Transferase activity	Unknown
PPA2273 cbac_12370	WP_002519568.1	Adenosine deaminase	DNA damage	Deaminase activity	Cytoplasm
gata cbac_06100	WP_002531385.1	Glutamyl-tRNA	Translation	Hydrolase activity	Cytoplasm
PPA1631 cbac_08855	WP_002517011.1	Thioesterase	Regulation of biological process	Catalytic activity	Cytoplasm
cbac_10785	WP_002530669.1	ATPase	Energy process	Hydrolase activity	Membrane
PPA1290 cbac_07010	WP_002531340.1	2,3-diaminopropionate biosynthesis protein SbnA	Biosynthetic process	Synthase activity	Cytoplasm
fmt HMPREF0675_4257	WP_002517988.1	Methionyl-tRNA formyltransferase	Translation	Transferase activity	Cytoplasm
tmk HMPREF0675_3289	WP_002517149.1	Thymidylate kinase	Biosynthetic process	Kinase activity	Cytoplasm
ung PPA0558 cbac_03120	WP_002519227.1	Uracil-DNA glycosylase	DNA repair	Glycosylase activity	Cytoplasm
PPA1277 cbac_06910	WP_002531349.1	ABC transporter substrate-binding protein	Transport Pathogenesis (Virulence)	Binding	Membrane
cbac_09495	WP_041444224.1	Phosphoesterase		Hydrolase activity	Cytoplasm
lysA PPA1259 cbac_06800	WP_002516817.1	Diaminopimelate decarboxylase	Biosynthetic process	Decarboxylase activity	Cytoplasm
rpoZ HMPREF1162_0201	WP_002516821.1	DNA-directed RNA polymerase subunit omega	Transcription	Polymerase activity	Nucleoid
HMPREF9578_00185	WP_002516610.1	ACT domain-containing protein	Metabolic process	Structural molecule activity	Cytoplasm
PPA0563 cbac_03150	WP_011183699.1	Conserved protein containing thioredoxin domain	Metabolic process	Reductase activity	Cytoplasm

cbac_01645	WP_002523010.1	PTS glucose transporter subunit IIB	Transport	Kinase activity	Membrane
PPA0548 cbac_03045	WP_002516725.1	Hydrolase, Ppx/GppA phosphatase family	Metabolic process	Hydrolase activity	Cytoplasm
PPA2167 cbac_11745	WP_002516352.1	Allantoate amidohydrolase (AAH, allantoinase)	Metabolic process	Hydrolase activity	Cytoplasm
PPA0814 cbac_04460	WP_002519094.1	Putative gluconeogenesis factor	Cell wall organization and cell shape	Transferase activity	Cytoplasm
map PPA1833 cbac_09965	WP_002523458.1	Methionine aminopeptidase	Protein processing	Peptidase activity	Cytoplasm
mfd cbac_03010	WP_002518816.1	Transcription-repair-coupling factor	Transcription	Binding	Cytoplasm
PPA1711 cbac_09310	WP_002522145.1	Short chain dehydrogenase	Lipid metabolism	Oxidoreductase activity	Cytoplasm
PPA1048 cbac_05685	WP_002515631.1	PglZ domain-containing protein	Cellular homeostasis	Catalytic activity	Cytoplasm
cbac_01755	WP_002518719.1	Sugar phosphate isomerase/epimerase	Metabolic process	Isomerase activity	Cytoplasm
cbac_02605	WP_002518777.1	Tat pathway signal protein	Transport	Translocase activity	Membrane
cbac_12735	WP_002518540.1	Chromosome partitioning protein ParB	DNA replication	Binding	Cytoplasm
dnaA HMPREF0675_3000	WP_002515747.1	Chromosomal replication initiator protein DnaA	DNA replication	Binding	Cytoplasm
rbpA PPA0820 cbac_04490	WP_002513867.1	RNA polymerase-binding protein RbpA	Transcription	Binding	Unknown
gatB HMPREF0675_4186	WP_002516598.1	Aspartyl-/glutamyl-tRNA	Translation	Transferase activity	Cytoplasm
pgl PPA1565 cbac_08515	WP_002521397.1	6-phosphogluconolactonase	Metabolic process	Phosphogluconolactonase activity	Unknown
PPA1083 cbac_05885	WP_002523969.1	Glycine cleavage system protein H	Metabolic process	Transferase activity	Membrane
ligA cbac_08830	WP_002531030.1	DNA ligase	DNA repair	Ligase activity	Cytoplasm
ligA cbac_08830	WP_002531030.1	DNA ligase	DNA replication	Ligase activity	Cytoplasm
purK PPA1702 cbac_09260	WP_002531235.1	N5-carboxyaminoimidazole ribonucleotide synthase.	Biosynthetic process	Synthase activity	Unknown
PPA1031 cbac_05600	WP_002515632.1	RNA polymerase principal sigma factor HrdD	Transcription	Binding	Cytoplasm
whiA HMPREF0675_3880	WP_002515546.1	Probable cell division protein WhiA	Cell division	Binding	Cytoplasm
cbac_01795	WP_002531193.1	Histidine phosphatase family protein	Regulation of biological process	Isomerase activity	Cytoplasm
cbac_02850	WP_002518803.1	Molybdopterin-guanine dinucleotide biosynthesis protein	Biosynthetic process	Binding	Cytoplasm
trpC PPA1130 cbac_06135	WP_002516614.1	Indole-3-glycerol phosphate synthase	Biosynthetic process	Synthase activity	Cytoplasm
cbac_00405	WP_002515702.1	ABC transporter ATP-binding protein	Transport	Binding	Membrane
PPA1364 cbac_07445	WP_002517908.1	IclR family transcriptional regulator	Transcription	Molecular function regulator	Cytoplasm
PPA0655 cbac_03620	WP_002515176.1	Antitoxin HicB	Response to stimulus	Binding	Unknown
PPA0055 cbac_00300	WP_002515807.1	DNA-binding response regulator	Transcription	Molecular function regulator	Nucleoid
rsmI PPA0524 cbac_02910	WP_002516667.1	Ribosomal RNA small subunit methyltransferase I	Response to stimulus	Transferase activity	Cytoplasm
PPA1824 cbac_09925	WP_009640388.1	Glycosyl transferase	Biosynthetic process	Transferase activity	Cytoplasm
PPA2237 cbac_12170	WP_002516470.1	1-acyl-sn-glycerol-3-phosphate acyltransferase	Biosynthetic process	Transferase activity	Cytoplasm
PPA1146 cbac_06210	WP_011183804.1	Beta-glucosidase	Metabolic process	Hydrolase activity	Cytoplasm
cbac_05620	WP_002515456.1	Alpha/beta hydrolase	Degradation	Hydrolase activity	Membrane
HMPREF0675_5088 cbac_06220	WP_002518085.1	Phosphomannomutase	Biosynthetic process	Hydrolase activity	Cytoplasm
cbac_06220	WP_041444150.1	Permease IIC component	Transport	Transferase activity	Membrane
PPA0082 cbac_00450	WP_002515718.1	Hypothetical membrane associated protein	Transport	Transporter activity	Membrane
rnhA PPA1729 cbac_09405	WP_002531248.1	Ribonuclease H	Metabolic process	Binding	Cytoplasm
PPA1898 cbac_10295	WP_002531304.1	Exodeoxyribonuclease III	DNA repair	Ribonuclease activity	Cytoplasm
PPA1069 cbac_05795	WP_002517916.1	Amino acid permease	Transport	Transporter activity	Membrane
PPA2185 cbac_11850	WP_002516309.1	Acyl dehydratase	Metabolic process	Isomerase activity	Cytoplasm

cbac_09895	WP_002525147.1	Glyco_hydro_35 domain-containing protein	Metabolic process	Hydrolase activity	Cytoplasm
cbac_06995	WP_002524911.1	Peptide synthetase	Biosynthetic process	Synthase activity	Cytoplasm
uvrB cbac_04410	WP_002518347.1	UvrABC system protein B	Response to stimulus	Binding	Cytoplasm
PPA1118 cbac_06075	WP_009640307.1	Methionine synthase vitamin-B12 independent	Biosynthetic process	Transferase activity	Cytoplasm
rsmG cbac_12765	WP_002518545.1	Ribosomal RNA small subunit methyltransferase G	Translation	Transferase activity	Cytoplasm
PPA0120 cbac_00670	WP_002530833.1	EXLDI protein	Unknown	Unknown	Unknown
PPA0624 cbac_03465	WP_002530925.1	N-acetyltransferase	Metabolic process	Transferase activity	Cytoplasm
PPA1166 cbac_06315	WP_002517766.1	Bifunctional	Metabolic process	Hydrolase activity	Cytoplasm
PPA2037 cbac_11045	WP_002514480.1	MerR family DNA-binding transcriptional regulator	Transcription	Molecular function regulator	Cytoplasm
PPA1186	WP_002513526.1	PPK2 domain-containing protein	Metabolic process	Kinase activity	Cytoplasm
PPA1616 cbac_08775	WP_002517026.1	DNA helicase	DNA replication	Hydrolase activity	Cytoplasm
PPA0348 cbac_01935	WP_002517076.1	Conserved protein, putative glycine cleavage T-protein	Metabolic process	Unknown	Unknown
PPA1488 cbac_08115	WP_002520231.1	Arabinose operon protein AraM	Biosynthetic process	Oxidoreductase activity	Cytoplasm
PPA1524 cbac_08315	WP_009640297.1	6-phosphogluconolactonase	Metabolic process	Phosphogluconolactonase activity	Cytoplasm
cbac_04925	WP_002515532.1	Isochorismate synthase	Biosynthetic process	Synthase activity	Cytoplasm
cobO PPA0437 cbac_02385	WP_002515069.1	Cob	Biosynthetic process	Transferase activity	Unknown
manA PPA0451 cbac_02480	WP_002517436.1	Mannose-6-phosphate isomerase	Metabolic process	Isomerase activity	Cytoplasm
PPA1085 cbac_05895	WP_002513631.1	MerR family transcriptional regulator	Transcription	Molecular function regulator	Cytoplasm
PPA2254 cbac_12250	WP_002516466.1	Amino acid permease	Transport	Transporter activity	Membrane
PPA0639 cbac_03540	WP_002530928.1	Glycogen synthase	Biosynthetic process	Transferase activity	Cytoplasm
PPA0177 cbac_00965	WP_002530809.1	APC family permease	Transport	Transporter activity	Membrane
cbac_12740	WP_002518541.1	ParA family protein	Cell division	Binding	Cytoplasm
PPA0685 cbac_03785	WP_002515306.1	Sialidase	Metabolic process	Sialidase activity	Cytoplasm
cobI PPA0420 cbac_02305	WP_002531167.1	Precorrin-2 C	Biosynthetic process	Transferase activity	Cytoplasm
PPA1464 cbac_07995	WP_009640171.1	Methylase	Translation	Transferase activity	Cytoplasm
nhaA HMPREF0675_3274	WP_002524662.1	Na	Cellular homeostasis	Transporter activity	Membrane
PPA2031 cbac_11015	WP_002530684.1	ABC transporter associated permease	Transport	Transporter activity	Membrane
mraY HMPREF9578_00542	WP_002513927.1	Phospho-N-acetylmuramoyl-pentapeptide-transferase	Cell wall organization and cell shape	Transferase activity	Membrane
HMPREF9578_00411	WP_002521769.1	Metallo-beta-lactamase domain protein	Regulation of biological process	Hydrolase activity	Cytoplasm
cbac_03830	WP_002523706.1	Cytochrome c oxidase assembly protein	Protein processing	Unknown	Membrane
PPA1365 cbac_07460	WP_011183848.1	CPBP family intramembrane metalloprotease	Protein processing	Peptidase activity	Membrane
PPA0557 cbac_03110	WP_002515113.1	Transporter	Transport	Transporter activity	Membrane
thiL PPA1357 cbac_07420	WP_002515338.1	Thiamine-monophosphate kinase	Biosynthetic process	Binding	Cytoplasm
cbac_11435	WP_002530754.1	Histidine kinase	Regulation of biological process	Kinase activity	Membrane
HMPREF0675_4955	WP_002515985.1	Enoyl-CoA hydratase/isomerase family protein	Unknown	Isomerase activity	Cytoplasm
tyrS cbac_07675	WP_009640057.1	Tyrosine--tRNA ligase	Translation	Ligase activity	Cytoplasm
thrC HMPREF0675_4320	WP_002518907.1	Threonine synthase	Biosynthetic process	Synthase activity	Cytoplasm
PPA1258 cbac_06795	WP_002517921.1	Homoserine dehydrogenase	Biosynthetic process	Dehydrogenase activity	Cytoplasm
ddl PPA1359 cbac_07430	WP_002531315.1	D-alanine--D-alanine ligase	Cell wall organization and cell shape	Ligase activity	Cytoplasm
PPA0109 cbac_00605	WP_011183602.1	Myosin-crossreactive antigen	Lipid metabolism	Binding	Cytoplasm
cbac_09270	WP_002517608.1	Peptidase E	Metabolic process	Peptidase activity	Cytoplasm

PPA2251 cbac_12235	WP_002518145.1	D-glycerate dehydrogenase	Metabolic process	Dehydrogenase activity	Cytoplasm
cbac_10845	WP_002518064.1	Dihydrodipicolinate synthase family protein	Biosynthetic process	Lyase activity	Cytoplasm
PPA1367 cbac_07470	WP_002516498.1	Thymidine phosphorylase	Metabolic process	Phosphorylase activity	Cytoplasm
purQ	WP_002514428.1	Phosphoribosylformylglycinamide synthase subunit PurQ	Biosynthetic process	Synthase activity	Cytoplasm
HMPREF9578_01524	WP_002517539.1	Conserved L-arabinose operon protein, hydrolase	Transcription	Hydrolase activity	Cytoplasm
PPA2322 cbac_12635	WP_002517793.1	ATP-grasp domain-containing protein	Energy process	Binding	Cytoplasm
PPA1285 cbac_06985	WP_002516449.1	AraC family transcriptional regulator	Transcription	Molecular function regulator	Cytoplasm
PPA2125 cbac_11505	WP_007401162.1	Polyphosphate	Transcription	Kinase activity	Cytoplasm
PPA1905 cbac_10330	WP_002531307.1	glucokinase/transcriptional regulator 2-oxoacid:ferredoxin oxidoreductase subunit beta	Metabolic process	Catalytic activity	Cytoplasm
cobF PPA1920	WP_002524506.1	Precorrin-6A synthase	Biosynthetic process	Synthase activity	Cytoplasm
cbac_10410	WP_002530734.1	Alpha-ketoacid dehydrogenase subunit beta	Response to stimulus	Dehydrogenase activity	Cytoplasm
PPA2093 cbac_11320	WP_002550711.1	Maleylpyruvate isomerase family	Metabolic process	Isomerase activity	Cytoplasm
murE PPA0753	WP_002518243.1	mycothiol-dependent enzyme UDP-N-acetylmuramoyl-L-alanyl-D-glutamate--2,6-diaminopimelate ligase	Biosynthetic process	Ligase activity	Cytoplasm
cbac_04150	WP_002515101.1	L-serine dehydratase	Metabolic process	Binding	Cytoplasm
PPA0396	WP_002520491.1	Transcriptional regulator	Transcription	Molecular function regulator	Cytoplasm
PPA1067 cbac_05785	WP_002514720.1	Biotin carboxylase	Lipid metabolism	Ligase activity	Cytoplasm
PPA1719 cbac_09355	WP_002516066.1	50S ribosomal protein L11	Translation	Structural molecule activity	Ribosome
rpIK	WP_002517298.1	Alpha-1,4 glucan phosphorylase	Metabolic process	Phosphorylase activity	Cytoplasm
HMPREF0675_4942	WP_002517307.1	Cobalt-precorrin-6A reductase	Biosynthetic process	Reductase activity	Cytoplasm
PPA0081 cbac_00440	WP_002531196.1	Uroporphyrinogen decarboxylase	Biosynthetic process	Decarboxylase activity	Cytoplasm
cbac_02400	WP_002514249.1	UPF0109 protein PPA1442	Unknown	Binding	Unknown
hemE cbac_01710	WP_002516303.1	ABC transporter ATP-binding protein	Transport	Transporter activity	Membrane
PPA1442 cbac_07865	WP_002517885.1	CTP synthase	Metabolic process	Binding	Cytoplasm
cbac_11690	WP_002551083.1	Threonylcarbamoyl-AMP synthase	Biosynthetic process	Binding	Cytoplasm
pyrG	WP_002521859.1	Glucokinase	Metabolic process	Kinase activity	Cytoplasm
HMPREF0675_4439	WP_002514221.1	50S ribosomal protein L20	Translation	Structural molecule activity	Ribosome
cbac_05930	WP_002516314.1	50S ribosomal subunit assembly factor BipA	Translation	Binding	Ribosome
PPA0722 cbac_03995	WP_002515744.1	Glycosyl transferase	Biosynthetic process	Transferase activity	Cytoplasm
rpIT	WP_002530735.1	Pyruvate dehydrogenase	Unknown	Oxidoreductase activity	Unknown
HMPREF9578_02089	WP_007400895.1	PTS sugar transporter	Transport	Transporter activity	Membrane
typA bipA PPA2003	WP_002531412.1	Carbamoyl-phosphate synthase large chain	Biosynthetic process	Synthase activity	Cytoplasm
cbac_10865	WP_002531205.1	Conserved protein, putative cell division inhibitor	Cell division	Catalytic activity	Cytoplasm
PPA0131 cbac_00730	WP_002515854.1	Glycosyltransferase family 4 protein	Unknown	Transferase activity	Cytoplasm
pdhA cbac_11325	WP_002524945.1	30S ribosomal protein S13	Translation	Structural molecule activity	Ribosome
cbac_02450	WP_002516467.1	ErfK/YbiS/YcfS/YnhG	Biosynthetic process	Transferase activity	Membrane
carB cbac_05435	WP_011183789.1	Conserved protein	Unknown	Binding	Unknown
PPA0286 cbac_01600	WP_002519002.1	RNA polymerase sigma factor SigA	Transcription	Binding	Cytoplasm
PPA0147 cbac_00815	WP_002516980.1	Energy-dependent translational throttle protein EttA	Translation	Transferase activity	Cytoplasm
cbac_06440	WP_002515739.1	Ribokinase	Metabolic process	Kinase activity	Cytoplasm
HMPREF0675_5340	WP_002519222.1	PhoH family protein	Unknown	Binding	Unknown
PPA1056 cbac_05725	WP_002531443.1	Hydroxyethylthiazole kinase	Biosynthetic process	Binding	Cytoplasm
sigA cbac_05605					
ettA PPA1636					
cbac_08880					
rbk PPA0018					
cbac_00095					
cbac_03165					
thiM PPA0885					

cbac_03675	WP_002519174.1	Glutamine synthetase	Biosynthetic process	Ligase activity	Cytoplasm
polA cbac_04270	WP_002523754.1	DNA polymerase I	DNA repair	Binding	Nucleoid
polA cbac_04270	WP_002523754.1	DNA polymerase I	DNA replication	Binding	Nucleoid
PPA0945 cbac_05135	WP_002526277.1	Putative histidine kinase	Regulation of biological process	Kinase activity	Membrane
cbac_12525	WP_002519762.1	Serine/threonine protein kinase	Regulation of biological process	Kinase activity	Cytoplasm
PPA0281 cbac_01575	WP_002517113.1	Conserved membrane spanning protein	Transport	Transporter activity	Membrane
radA PPA0312 cbac_01740	WP_002517527.1	DNA repair protein RadA	DNA repair	Hydrolase activity	Cytoplasm
PPA0342 cbac_01905	WP_002517143.1	Conserved protein	Unknown	Hydrolase activity	Cytoplasm
PPA1639 cbac_08895	WP_002524831.1	ABC transporter	Transport	Transporter activity	Membrane
PPA2096 cbac_11340	WP_009639878.1	Molybdenum cofactor biosynthesis enzyme/coproporphyrinogen III oxidase	Biosynthetic process	Catalytic activity	Cytoplasm
cbac_04120	WP_002518266.1	DUF58 domain-containing protein	Unknown	Structural molecule activity	Membrane
PPA0710 cbac_03930	WP_002530941.1	Cytochrome bc1 complex cytochrome b subunit	Unknown	Reductase activity	Membrane
hrcA HMPREF9578_00410	WP_002513807.1	Heat-inducible transcription repressor HrcA	Response to stimulus	Binding	Cytoplasm
PPA0072 cbac_00395	WP_002525540.1	Membrane associated protein	Transport	Transporter activity	Membrane
PPA2298 cbac_12500	WP_002515857.1	Conserved protein, putative mechanosensitive ion channel	Transport	Transporter activity	Membrane
PPA0732 cbac_04045	WP_002513952.1	Geranylgeranyl pyrophosphate synthase	Biosynthetic process	Transferase activity	Cytoplasm
PPA1671 cbac_09095	WP_002522165.1	Dihydrofolate reductase	Metabolic process	Reductase activity	Cytoplasm
PPA1917 cbac_10395	WP_002515372.1	Hypothetical membrane protein	Transport	Transporter activity	Membrane
PPA0434	WP_002517347.1	ABC transporter ATP-binding protein	Transport	Transferase activity	Membrane
PPA1476 cbac_08060	WP_002516879.1	Glycine betaine transport system permease protein	Transport	Transporter activity	Membrane
PPA1955 cbac_10590	WP_002524492.1	Right-handed parallel beta-helix repeat-containing protein	Unknown	Catalytic activity	Unknown
cbac_04030	WP_002521854.1	Non-specific serine/threonine protein kinase	Regulation of biological process	Kinase activity	Cytoplasm
nuoH HMPREF9578_02182	WP_002514928.1	NADH-quinone oxidoreductase subunit H	Unknown	Oxidoreductase activity	Membrane
cbac_00710	WP_002526015.1	DUF2029 domain-containing protein	Unknown	Structural molecule activity	Membrane
PPA0128 cbac_00715	WP_011183607.1	Membrane spanning protein	Biosynthetic process	Transferase activity	Membrane
PPA2033 cbac_11025	WP_002530685.1	Amino acid permease	Transport	Transporter activity	Membrane

Table S2. List of proteins identified exclusively in *C. acnes*-derived H1 EVs under anaerobic conditions

Gene name	Accession number	Protein name	GO - Biological process	GO - Molecular function	GO - Cellular component
HMPREF9578_00571	WP_002521853.1	Ribonuclease	Cellular homeostasis	Ribonuclease activity	Cytoplasm
pdxA cbac_01665	WP_002531202.1	4-hydroxythreonine-4-phosphate dehydrogenase PdxA	Biosynthetic process	Oxidoreductase activity	Cytoplasm
folE PPA0261 cbac_01480	WP_002517093.1	GTP cyclohydrolase 1	Metabolic process	Binding	Cytoplasm
PPA0503 cbac_02790	WP_002518798.1	Helix-turn-helix domain-containing protein	Regulation of biological process	Binding	Unknown
mmsA PPA0461 cbac_02540	WP_002531156.1	Methylmalonate-semialdehyde dehydrogenase	Metabolic process	Dehydrogenase activity	Cytoplasm
PPA1815 cbac_09865	WP_002517606.1	3-oxoacyl-ACP reductase FabG	Lipid metabolism	Reductase activity	Cytoplasm
PPA1609 cbac_08735	WP_002531040.1	Conserved phage-associated protein	Unknown	Unknown	Unknown
PPA2063 cbac_11190	WP_002530709.1	Peptide ABC transporter substrate-binding protein	Transport	Transporter activity	Membrane
PPA0851 cbac_04650	WP_002531018.1	ATP-dependent endonuclease	DNA repair	Hydrolase activity	Cytoplasm
PPA0144 cbac_00800	WP_011183610.1	DeoR/GlpR transcriptional regulator	Transcription	Molecular function regulator	Nucleoid
PPA1638 cbac_08890	WP_002531028.1	ABC transporter	Transport	Transporter activity	Membrane
PPA2091 cbac_11310	WP_002530732.1	ABC transporter ATP-binding protein	Transport	Transporter activity	Membrane
PPA1760 cbac_09575	WP_002514763.1	ABC transporter associated permease	Transport	Transporter activity	Membrane
PPA0399 cbac_02205	WP_002531171.1	Sugar ABC transporter	Transport	Transporter activity	Membrane
PPA1147 cbac_06215	WP_002513567.1	PTS sugar transporter subunit IIB	Transport	Kinase activity	Membrane
PPA1915 cbac_10385	WP_002518040.1	ABC transporter ATP-binding protein	Energy process	Binding	Membrane
cbac_02210	WP_002517551.1	Carbohydrate ABC transporter permease	Transport	Transporter activity	Membrane
PPA0925 cbac_05045	WP_002513798.1	Putative two-component system sensor kinase	Response to stimulus	Kinase activity	Membrane
PPA1599 cbac_08685	WP_007400937.1	CAAX protease	Protein processing	Peptidase activity	Membrane
PPA1389 cbac_07600	WP_002516495.1	NUDIX hydrolase	Cellular homeostasis	Hydrolase activity	Cytoplasm
PPA1721 cbac_09365	WP_002522139.1	Dihydrolypoamide dehydrogenase	Cellular homeostasis	Dehydrogenase activity	Cytoplasm
iolB PPA0458 cbac_02525	WP_002531157.1	5-deoxy-glucuronate isomerase	Metabolic process	Isomerase activity	Cytoplasm
PPA0398 cbac_02200	WP_002520024.1	Conserved protein, putative sugar-binding protein	Regulation of biological process	Binding	Membrane
cbac_10405	WP_002519594.1	CoA ester lyase	Unknown	Lyase activity	Unknown
PPA1529 cbac_08340	WP_002516971.1	Conserved protein	Unknown	Unknown	Membrane
moaC PPA0498 cbac_02765	WP_007401059.1	Cyclic pyranopterin monophosphate synthase	Biosynthetic process	Synthase activity	Cytoplasm
menB PPA0907 cbac_04940	WP_002513816.1	1,4-dihydroxy-2-naphthoyl-CoA synthase	Biosynthetic process	Synthase activity	Cytoplasm
PPA1229 cbac_06650	WP_002517946.1	ArsR family transcriptional regulator	Transcription	Molecular function regulator	Cytoplasm
PPA1086 cbac_05900	WP_002517877.1	Bifunctional nuclease family protein	Protein processing	Hydrolase activity	Nucleoid
PPA2112 cbac_11430	WP_002530753.1	DNA-binding response regulator	Transcription	Binding	Nucleoid
PPA1459 cbac_07975	WP_002514269.1	Alpha-mannosidase	Metabolic process	Binding	Cytoplasm
PPA1050 cbac_05695	WP_011183787.1	Conserved protein	Unknown	Unknown	Unknown
PPA0062 cbac_00345	WP_002530850.1	Alpha-mannosidase	Metabolic process	Binding	Cytoplasm
aceE cbac_05385	WP_002525003.1	Pyruvate dehydrogenase E1 component	Metabolic process	Dehydrogenase activity	Cytoplasm
PPA2267 cbac_12320	WP_002519750.1	6-phosphofructokinase	Metabolic process	Kinase activity	Cytoplasm
topA PPA0241 cbac_01375	WP_002529762.1	DNA topoisomerase 1	DNA replication	Binding	Nucleoid
nadE PPA2266 cbac_12310	WP_002518158.1	Glutamine-dependent NAD	Biosynthetic process	Synthase activity	Cytoplasm
PPA1142 cbac_06190	WP_002521618.1	PTS system, sucrose-specific IIBC component	Transport	Transferase activity	Membrane
cbac_04110	WP_002530961.1	DUF3040 domain-containing protein	Unknown	Unknown	Membrane
aroC cbac_06400	WP_002517990.1	Chorismate synthase	Biosynthetic process	Synthase activity	Cytoplasm

cbac_10960	WP_002519475.1	MFS transporter	Transport	Transporter activity	Membrane
gnpA PPA0083 cbac_00455	WP_002530846.1	1,3-beta-galactosyl-N-acetylhexosamine phosphorylase	Metabolic process	Phosphorylase activity	Cytoplasm
PPA2320 cbac_12625	WP_002517435.1	L-arabinose utilization protein, glycerol dehydrogenase	Lipid metabolism	Oxidoreductase activity	Cytoplasm
PPA0290 cbac_01620	WP_002517197.1	Putative two-component sensor kinase	Response to stimulus	Structural molecular activity	Membrane
ctaD PPA0702 cbac_03885	WP_002518277.1	Cytochrome c oxidase subunit 1	Transport	Binding	Membrane
PPA2203 cbac_11960	WP_002518166.1	Putative Na ⁺ /H ⁺ antiporter	Transport	Transporter activity	Membrane
PPA1315 cbac_07150	WP_009640225.1	Exodeoxyribonuclease V gamma chain	DNA repair	Ribonuclease activity	Cytoplasm
cbac_10755	WP_002523368.1	Pyridine nucleotide-disulfide oxidoreductase	Cellular homeostasis	Oxidoreductase activity	Nucleoid
PPA1610 cbac_08740	WP_002531039.1	Putative transcriptional regulator	Transcription	Binding	Nucleoid
PPA0416 cbac_02280	WP_011183669.1	DNA-binding response regulator	Transcription	Binding	Nucleoid
PPA2216 cbac_12040	WP_002514161.1	Acyl-CoA dehydrogenase	Lipid metabolism	Dehydrogenase activity	Cytoplasm
PPA1273 cbac_06890	WP_002516865.1	ABC transporter ATP-binding protein	Transport	Transporter activity	Membrane
cbac_02265	WP_002517453.1	ABC transporter ATP-binding protein	Transport	Transporter activity	Membrane
cobA PPA0439 cbac_02395	WP_002517252.1	Uroporphyrinogen III methylase	Biosynthetic process	Transferase activity	Cytoplasm
argC HMPREF0675_4395	WP_002520173.1	N-acetyl-gamma-glutamyl-phosphate reductase	Biosynthetic process	Reductase activity	Cytoplasm
PPA2088 cbac_11295	WP_002530729.1	Esc family protein	Unknown	Unknown	Membrane
rsmH cbac_04135	WP_002530963.1	Ribosomal RNA small subunit methyltransferase H	Translation	Transferase activity	Cytoplasm
PPA1217 cbac_06590	WP_002518927.1	4-hydroxybutyrate coenzyme A transferase	Metabolic process	Transferase activity	Cytoplasm
PPA0141 cbac_00780	WP_002530823.1	HPr family phosphocarrier protein	Transport	Transferase activity	Cytoplasm
PPA2240 cbac_12185	WP_002530896.1	Cation-transporting ATPase	Transport	Transporter activity	Membrane
HMPREF0675_5099	WP_002516194.1	TrkA C-terminal domain protein	Transport	Transporter activity	Membrane
PPA1732 cbac_09420	WP_002531250.1	ABC transporter associated permease	Transport	Transporter activity	Membrane
PPA0540 cbac_03005	WP_002516643.1	Conserved protein // PrsW family intermembrane metalloprotease	Regulation of biological process	Peptidase activity	Membrane
PPA0068 cbac_00375	WP_002519827.1	Putative two component sensor kinase	Response to stimulus	Kinase activity	Membrane
PPA1275 cbac_06900	WP_002516777.1	ABC transporter permease	Transport	Transporter activity	Membrane

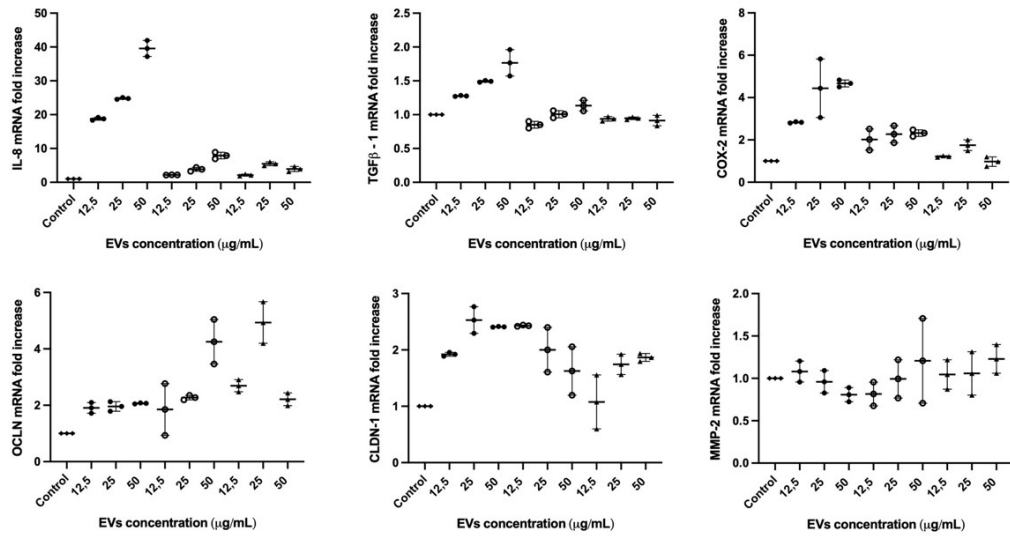
Table S3. List of proteins identified exclusively in *C. acnes*-derived H2 EVs under anaerobic conditions

Gene name	Accession number	Protein name	GO - Biological Process	GO - Molecular function	GO - Cellular component
PPA1345 cbac_07350	WP_002517702.1	DUF1707 domain-containing protein	Unknown	Unknown	Membrane
HMPREF0675_3894	WP_002515660.1	Uncharacterized protein	Unknown	Unknown	Membrane
rpsT HMPREF0675_3956	WP_002515457.1	30S ribosomal protein S20	Translation	Structural molecular activity	Ribosome
PPA0522 cbac_02900	WP_011183691.1	Nitrate reductase	Energy process	Transporter activity	Membrane
PPA0960 cbac_05215	WP_002517830.1	MsnO8 family LLM class oxidoreductase	Regulation of biological process	Oxidoreductase activity	Membrane
PPA0960 cbac_05215	WP_002517830.1	MsnO8 family LLM class oxidoreductase	Response to stimulus	Oxidoreductase activity	Cytoplasm
PPA0724 cbac_04005	WP_002530950.1	1-acyl-sn-glycerol-3-phosphate acyltransferase	Lipid metabolism	Transferase activity	Cytoplasm
hisB HMPREF9578_0015 0	WP_002513559.1	Imidazoleglycerol-phosphate dehydratase	Byosynthetic process	Lyase activity	Cytoplasm
kup cbac_11865	WP_002519550.1	Probable potassium transport system protein kup	Transport	Transporter activity	Membrane
uppP HMPREF0675_5297	WP_002516473.1	Undecaprenyl-diphosphatase	Cell wall organization and cell shape	Phosphatase activity	Membrane
PPA0619 cbac_03440	WP_002530923.1	Allantoin permease	Transport	Transporter activity	Membrane

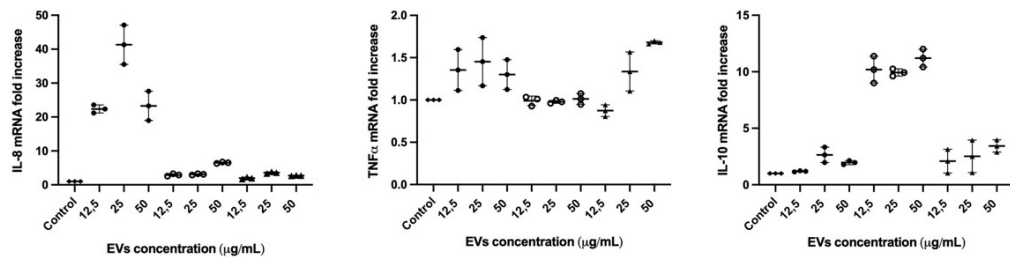
Table S4. List of primer sequences used for RT-qPCR

Genes		Primers (From 5' to 3')
CREBBP	FWD	5' GAGAGCAAGCAAACGGAGAG
	RV	5' AAGGGAGGCAAACAGGACA
TNF α SEB	FWD	5' CCAGGGACCTCTCTCTAATCA
	RV	5' TCAGCTTGAGGGTTTGCTAC
IL-6 SEB	FWD	5' ACTCACCTCTTCAGAACGAATTG
	RV	5' AGCCATCTTTGGAAGGTTTCAG
IL-8 SEB	FWD	5' CTTGGCAGCCTTCTGATTT
	RV	5' GGGTGAAAGGTTTGGAGTATG
PLIN 2	FWD	5' TCAGCTCCATTCTACTGTTCCACC
	RV	5' CCTGAATTTTCTGATTGGCACT
TGF β 1	FWD	5' TACCTGAACCCGTTGCTCTC
	RV	5' GTTGCTGAGGTATCGCCAGGAA
COX-2	FWD	5' GAATCATTACCAGGCAAATTG
	RV	5' TCTGTAAGCGGGTGAACA
OCLN	FWD	5' GTCATCCAGGCCTTTGAAA
	RV	5' GGTGATAATGATTCCGTTTG
MMP2	FWD	5' AGCGAGTGGATGCCGCCTT
	RV	5' CATTCCAGGCATCTGCGAT
CLDN1	FWD	5' GTCTTTGACTCCTTGTGAATCTG
	RV	5' CACCTCATCGTCTTCCAAGCAC
IL-10	FWD	5' TCTCCGAGATGCCTTCAGCAGA
	RV	5' TCAGACAAGGCTTGGCAACCCA

(A) HaCaT



(B) Jurkat



(C) SZ95

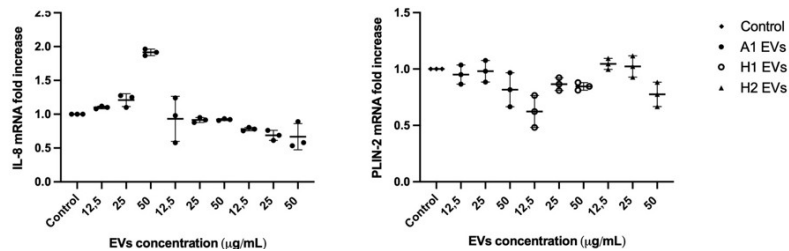


Figure S1. *In vitro* analysis with direct incubation of *C. acnes* EVs. Human cells were treated for 24h with different concentrations (12.5, 25 and 50 µg/mL) of *C. acnes* A1, H1 and H2 EVs. Total RNA was extracted, and different biomarkers were assessed by RT-qPCR. (A) HaCaT (B) SZ95 and (C) Jurkat immortalized cell lines. All data are presented as individual dots of experimental replicates ± standard deviation (SD) of triplicate measurements (* $p \leq 0.05$, ** $p \leq 0.001$ versus non-stimulated controls).

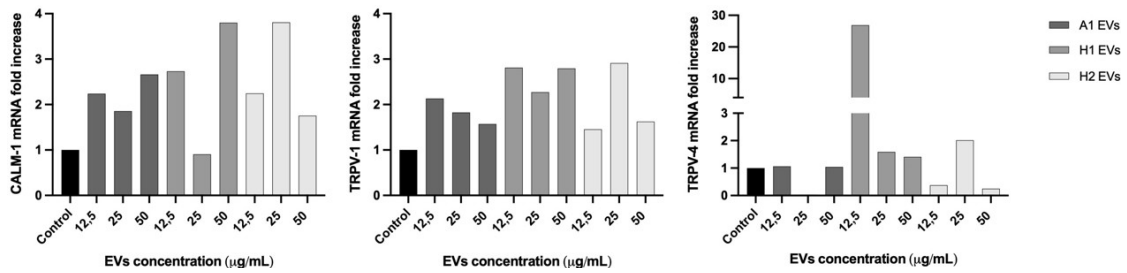


Figure S2. *In vitro* analysis with direct incubation of *C. acnes* EVs with CALM-1, TRPV-1, and TRPV-4 biomarkers. HaCaT cells were treated for 24h with different concentrations (12.5, 25 and 50 µg/mL) of *C. acnes* A1, H1 and H2 EVs. Total RNA was extracted, and different biomarkers were assessed by RT-qPCR.

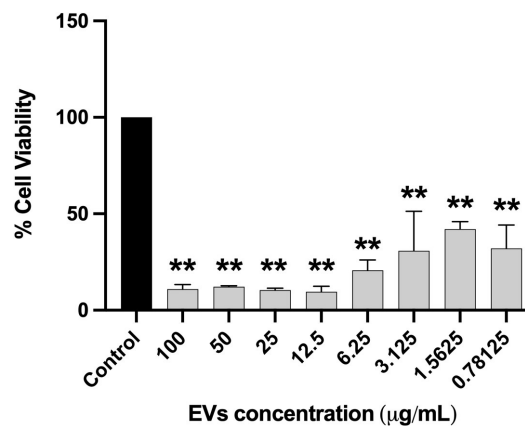


Figure S3. Cell viability assay of HaCaT cells incubated with ExoGAG. Different concentrations of pure ExoGAG (IDIS Nasasbiotech) were tested in an *in vitro* skin model of HaCaT cells to study the tolerance of this product as an alternative method to precipitate and isolate EVs. All data are presented as mean \pm standard deviation (SD) of triplicate measurements (** $p \leq 0.001$ versus non-stimulated controls).

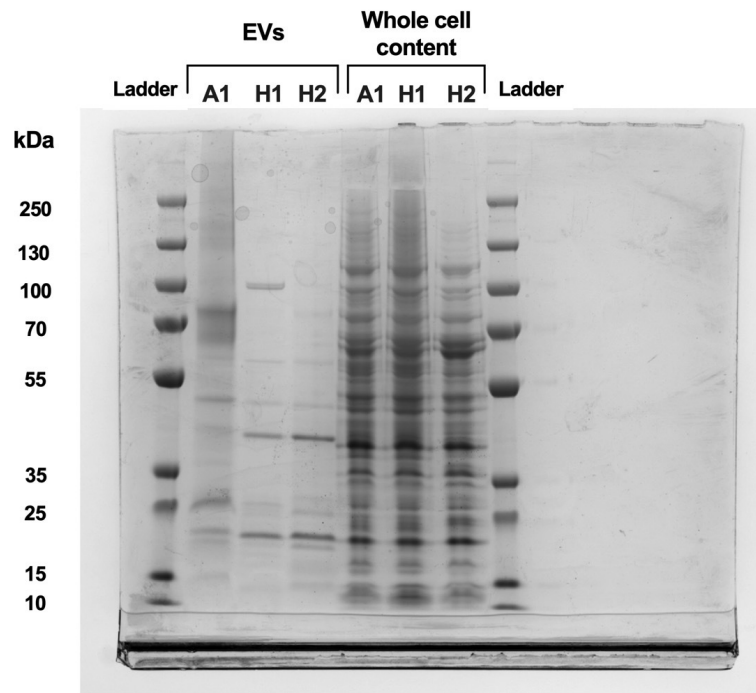


Figure S4. SDS Gel. Protein profile of *C. acnes* A1, H1 and H2. Both EVs and whole cell content fractions are represented.